Systemic Blood Pressure in the Obstructive Sleep Apnoea/Hypopnoea Syndrome.

Dr Jacqueline Frances Faccenda

MBChB MRCP

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Department of Medicine

University of Edinburgh

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Abstract.

The obstructive sleep apnoea hypopnoea syndrome (OSAHS) is a common disorder, affecting 1-4 % of the middle-aged population. The consequences of OSAHS include an impact on sleepiness, health status, cognitive function and driving. There has been conflicting data in the literature concerning the impact of sleep apnoea on arterial blood pressure (BP). Apnoeas and hypopnoeas are associated with acute swings in nocturnal BP of up to 100 mmHg. However whether sleep apnoea leads to sustained daytime hypertension was unresolved. Early uncontrolled studies by Guilleminault in the 1970's showed BP in severe OSAHS returning to normal levels after tracheostomy, and this was later echoed by Sullivan using CPAP to treat the disorder. Later studies however suggested that the association between these two disorders was as a result of common confounding factors in OSAHS rather than the disorder having a true causal role in hypertension. Young et al in the early 1990's, looked at a subset of their large epidemiological group, the Wisconsin Sleep cohort, and showed the prevalence of hypertension was higher in patients with sleep disordered breathing compared to matched controls. More recently Brooks using chronically instrumented dogs as a model of OSAHS, showed systemic BP was elevated in the daytime when they simulated sleep apnoea, and this resolved back to normal levels over a period of several days to weeks when the apnoeas were stopped. This study provided convincing evidence that sleep apnoea caused elevated BP, which persisted during waking hours, at least in dogs.

The purpose of this thesis was to demonstrate in a randomised controlled trial whether BP was higher in untreated OSAHS. The study was crossover in design with the patients acting as their own controls so increasing the power of the study. Sixty-eight patients were studied with at least two major symptoms of OSAHS, and a mean AHI

of ≥15 events/hour slept and a mean age of 49 years (27-72). During the study, mechanisms for the elevated BP were looked for, with a sub-set of patients taking part in a further study looking at baroreceptor sensitivity. Urinary microalbumin was also studied in a smaller cohort looking to see if this simple test could be used as an easy marker to predict the patient group who were most at risk of renal and cardiovascular disease. Health status and cognitive function were also measured, to confirm the health benefits of treating this patient group with CPAP compared to an oral placebo. Diastolic Blood Pressure (DBP) was reduced by CPAP in patients with OSAHS. The data were analysed on an intention to treat basis, including all 68 patients including poorly compliant patients. This showed a 1.5 mmHg drop in DBP ($p = 0.04$) with CPAP. In an *a priori* compliant subset (CPAP use ≥ 3.5 hours/night) DBP remained significantly lower by a magnitude of 1.9 mmHg ($p = 0.03$). In the other *a priori* subset of severely hypoxaemic patients (4% desaturation index ≥ 20/hour) there were also falls in Systolic BP (4.0 mmHg, $p = 0.009$), DBP (5.0 mmHg, $p = 0.002$) and mean arterial pressure (3.4 mmHg, $p = 0.012$). Although all the reductions in pressures were small, data from population studies suggest such reductions may be associated with significant health benefits. In addition the effects may have been underestimated as the equipment used to measure BP may cause an arousal from sleep there by artificially elevating the night-time BP recorded. The baroreceptor function was not different between the two treatments. The urinary microalbumin was abnormal in 35% of the patient group, the reasons for this needs further investigation. The benefits found in quality of life confirmed previous studies although this is the first randomised controlled trail to show benefits in the Functional Outcomes of Sleep Questionnaire. The lack of improvement in the neuropsychological testing may reflect the tests used. The CPAP compliance on this study was less than ideal, but

similar to those in other prospective studies.

This thesis reports the first randomised controlled trial in OSAHS patients to show a reduction in BP with CPAP therapy. The mechanisms require further study.

'It is a good thing for an uneducated man to read books of quotations. The quotations, when engraved upon the memory, give you good thoughts. They also make you anxious to read the authors and look for more.'

Sir Winston Churchill

'Thoroughness is the most difficult habit to acquire, but it is the pearl of great price, worth all the worry and of the search.'

Sir William Osler

Declaration.

I declare that I have been the principal investigator in all the studies presented in this thesis and that the contents of this thesis are my own work. Various members of sleep centre staff whose contributions have been noted in the acknowledgements section have assisted me in aspects of these studies.

The work was performed in the sleep centre within the Royal Infirmary of Edinburgh and in patient's homes between 1997 and 1999.

Dr J F Faccenda

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Abbreviations.

ABPM	Ambulatory blood pressure monitor
ADR	Adrenaline
AHI	Apnoea hypopnoea index
AI	Apnoea index
ANP	Atrial natriuretic peptide
ANS	Autonomic nervous system
BP	Blood pressure
BRS	Baroreflex sensitivity
CPAP	Continuous positive airway pressure
DBP	Diastolic blood pressure
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
ENT	Ear nose and throat
EOG	Electro oculogram
ET-1	Endothelin 1
FFT	Fast Fourier transformation
FOSQ	Functional outcomes of sleep questionnaire
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
IHD	Ischaemic heart disease
IOD	Intra oral device

LF	Low frequency
LV	Left ventricle
MAP	Mean arterial pressure
MAD	Mandibular advancement device
MI	Myocardial infarction
MNSA	Muscle sympathetic nervous activity
MRS	Mandibular repositioning splint
MRI	Magnetic resonance imaging
MSLT	Multiple sleep latency test
MWT	Maintenance of wakefulness test
NA	Noradrenaline
NO	Nitric oxide
OR	Odds ratio
OSAS	Obstructive sleep apnoea syndrome
PC	Personal computer
PI	Pulse interval
PIp	Pulse interval power
PLM's	Periodic limb movements
PP	Pulse pressure
PSG	Polysomnogram
RDI	Respiratory disturbance index
RR	Relative risk
QoL	Quality of life
RCT	Randomised controlled trial
SAHS	Sleep apnoea/hypopnoea syndrome

SAQLI	Sleep apnoea quality of life index
SAS	Sleep apnoea syndrome
SBP	Systolic blood pressure
SDB	Sleep disordered breathing
SF-36	Short form 36
SHHS	Sleep heart health study
SNS	Sympathetic nervous system
SWS	Slow wave sleep
TGFβ	Tissue growth factor β
UARS	Upper airways resistance syndrome
U3P	Uvulopalatopharyngoplasty
VEGF	Vascular endothelial growth factor
VLF	Very low frequency

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Chapter 1.

Obstructive Sleep Apnoea/Hypopnoea Syndrome and its Treatment.

1.1 Introduction.

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) was only recognised relatively recently but has been extensively researched in the last 30 years. It has an estimated prevalence of 1-2% of middle aged women and 2-4% of middle aged men[1]. The disorder is characterised by recurrent upper airway collapse during sleep[2], causing arousal from sleep with associated hypoxaemia and sleep fragmentation.

The consequences of this disorder are multiple and include excessive daytime sleepiness [3], cognitive dysfunction [4], and a reduction in psychological well being [5]. The physiological consequences are complex, including cardio-respiratory disturbances, with night-time hypertension being well documented [6-15], however whether OSAHS itself leads to daytime hypertension remains unclear and is the main focus of this thesis.

1.2 History.

In 1837 in 'The Posthumous Papers of the Pickwick Club' Charles Dickens described a very obese boy called Joe with hypersomnolence. There are earlier references in the literature referring to particularly sleepy people who probably had OSAHS or Narcolepsy. Caton in 1889 and Lamacq in 1897 both observed that some

'narcoleptics' suffered obstructed airways during sleep. However it was Sir William Osler in 1918 that first used the term 'Pickwickian' to refer to his obese hypersomnolent patients. Kerr and Lagen first reported the significant cardiovascular sequelae of the disorder in 1936. In the 1950's Burwell classically described the disorder, with a combination of obesity, hypersomnolence, periodic breathing, hypoventilation and cor pulmonale. Sleep medicine was brought to the fore by Gastaut et al in 1965 when they observed sleeping patterns with renewed interest, and noted multiple pauses [16] in 'Pickwickian' patients. Jung et al followed this up later that year with a case report describing the physiology further [17]. The term Sleep Apnoea Syndrome (SAS) was coined in 1972 after the first symposium on sleep and related respiratory problems led by Sadoul and Lugaresi [18]. Hypopnoeas were first described by Block et al in 1979, and it was recognised that the hypopnoeas noted were also of clinical significance [19], therefore the term sleep apnoea/hypopnoea syndrome (SAHS) was used. To clarify the obstructive nature of the disorder, this term has been added to the name to become obstructive sleep apnoea/hypopnoea syndrome (OSAHS).

1.3 Definitions.

The definitions in OSAHS remain a subject of debate, it is generally accepted that apnoea is a cessation of breathing at both nose and mouth for >10 seconds; and hypopnoea is a reduction in tidal volume by > 50% or a reduction in flow rate of > 50% [20,21] plus or minus at least a 4% arterial oxygen desaturation (in the recent classifications the desaturation has been removed from the definition of hypopnoea

[20]). Arousal is defined by a return of alpha or theta rhythm in the EEG of ≥1.5 seconds and a rise in EMG activity during this period. The definition of sleep apnoea syndrome itself is difficult as many normal people have 10-second apnoeas with normal oxygen saturation as shown by Block et al [22].

In 1966 Gastaut et al distinguished three types of sleep apnoea [23]:

- **Central:** defined by cessation of airflow past nasal and buccal thermistors and cessation of respiratory movements from both thoracic and abdominal strain gauges.
- **Obstructive:** airflow past the nasal and buccal thermistors is absent in spite of respiratory effort noted with the abdominal and thoracic strain gauges.
- **Mixed:** cessation of airflow throughout and absence of any respiratory effort in the early part followed by resumption of the respiratory effort.

Guilleminault et al suggested that the criterion of 5 or more events per hour, apnoea index (AI), was used to define obstructive sleep apnoea syndrome (OSAS) in 1976 [24,25]. The use of an event frequency of > 5 per hour slept as a diagnostic criterion was affirmed with epidemiological studies by Young et al, suggesting that the consequences of OSAHS were evident at this level of disturbance. The combined number of apnoeas and hypopnoeas divided by the total sleep time in hours calculates the apnoea hypopnoea index (AHI).

With further research it has been realised that many people have disturbed breathing during sleep. The significance of this so-called sleep disordered breathing (SDB) is still unclear in many populations.

Respiratory disturbance index (RDI) is a term that has been used more recently to report the number of respiratory events per hour slept. It may be that the alleged 'gold standard' investigation (polysomnography) that is used in the study of sleepy patients may not be measuring all the pathophysiologically important variables. Research continues to look at different methods for investigating this disorder.

1.4 Physiology of Normal Sleep.

With the onset of sleep the heart rate drops, cardiac output falls, respiration slows, and muscle tone is reduced. Sleep is a reversible physiological and behavioural state, which has two main divisions: rapid eye movement (REM) and non rapid eye movement (NREM) sleep.

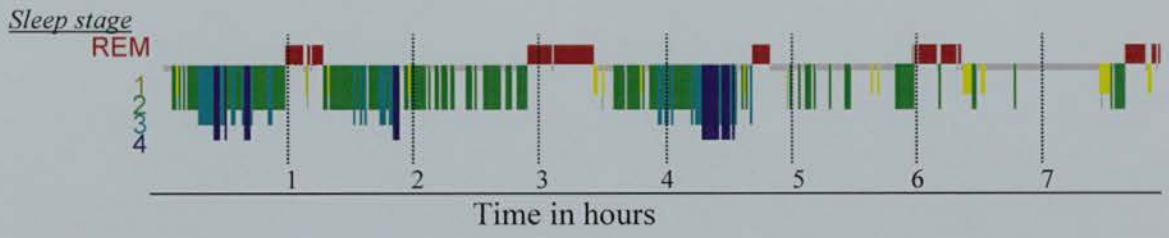
REM sleep is characterised by brief phasic bursts of eye movement present on a background of tonic changes, and is associated with a state of cerebral activation. Blood pressure, heart rate and respiratory rate all vary markedly during REM sleep. Afferent sensory and efferent motor activities are both markedly inhibited in REM sleep. REM is the sleep state associated with dreaming.

NREM sleep encompasses all other sleep stages outside REM. It is categorised into 4 stages, identified using the electroencephalogram (EEG), electromyogram and electro-oculogram. In NREM Stage 2 sleep the EEG shows characteristic sleep spindles and K complexes. Slow waves increasingly dominate the EEG as Stage 3 progresses to Stage 4, often referred to as slow wave sleep (SWS), Stage 0 is wakefulness.

There are usually 5-6 sleep cycles a night with decreasing cycle length as the night

progresses. The sleep cycle comprises wake to stage 1 all the way through to stage 4, then an episode of REM sleep occurring approximately 90 minutes after sleep onset. This pattern cycles through the night with the periods of REM sleep gradually getting longer, so that SWS predominates early and REM sleep later in the night [26]. After the sleep study is scored the sleep stages are charted on a hypnogram, an example of this is included in figure 1.1 below.

Figure 1.1: Example of Hypnogram.



Legend:
REM sleep - red
Stage 1 sleep - yellow
Stage 2 sleep - green
Stage 3 sleep - turquoise
Stage 4 sleep - green

1.5 Aetiology.

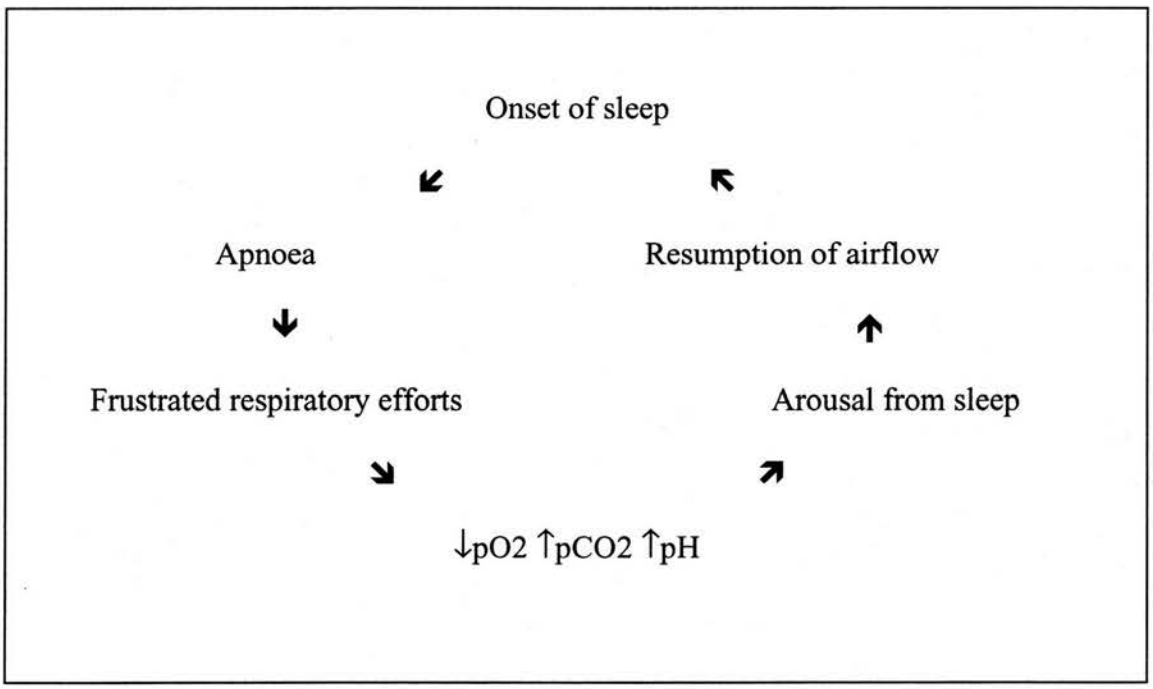
OSAHS is due to obstruction of the upper airway during sleep. The upper airway of patients with OSAHS is already narrow before sleep. Obesity is a contributing factor to this airway narrowing in about half of patients [27]. Other predisposing factors include male gender, middle age, genetic predisposition and anatomic susceptibility due to retrognathia or anatomical obstruction of the pharynx.

When the patient goes to sleep the activity of the upper airway dilating muscles decrease and so the airway narrows then closes, resulting in hypopnoeas and apnoeas

respectively. This results in arousal from sleep, often only for fractions of a second but sufficient to allow the airway to open once more and then the patient drifts back to sleep once more, and the cycle begins again. This results in sleep fragmentation and poor sleep quality.

Figure 1.2: Cycle of Events in OSAHS.

OSAHS arises from a sequence of events, which form a recurring cycle.



1.6 Genetics.

Strohl presented a family who all had OSAHS, surmising that there may be a genetic component to this disorder, which sparked further research in this area [28]. Familial studies, including twin data suggest that there is a genetic predisposition for the

disorder [29,30]. Lavie studied 45 patients' relatives and showed a higher prevalence of OSAHS and snoring compared to the normal population [31]. He concluded that there may be an element of inheritance in the disorder, however his study lacked a matched control population. Around the same time from our own centre Mathur et al studied first degree relatives of non obese patients with OSAHS, showing that 25% of them had an AHI > 15 events per hour slept. No control group was included in this pilot study; they utilised the data published by the Oxford group looking at the prevalence in 893 middle-aged men for comparison [32]. The authors concluded that there was a strong familial component in this disorder and that further work needed to be done in this area [33]. Mathur went on to perform a further study with 51 first-degree relatives of non-obese patients with OSAHS with a carefully matched control population. This study showed a significantly higher prevalence of SDB in the relatives than in the control population. There were differences in the facial structure with OSAHS relatives having retroposition of the maxillae and mandibles detected using cephalometry. The authors concluded that there was a strong familial component to OSAHS and this may be in part due to the facial structure [34]. This work was paralleled by work from Guilleminault who also concluded that there was a strong familial element to the disorder and that the craniofacial features must have a part to play in the aetiology of the disorder [35]. There has been as yet no specific gene identified to be the casual agent in the development of OSAHS, a disorder which is almost certainly polygenic.

1.7 Gender Differences.

It is not understood why 85% of diagnosed cases are male. Initial studies suggested that there was a large difference between the sexes in prevalence of the disorder [22]. The more recent epidemiological studies suggest that the prevalence in women is half that seen in men, outpatient clinics are as yet to reflect this [1,36,37]. It may be a reflection of the different presentations, referral patterns and expectations of the different sexes. However very little is known about the sex differences in relation to the pathogenesis of the disorder. Several studies have demonstrated the gender differences in the anatomy and physiology of the upper airway suggesting pathological differences between the sexes [38-40]. Why these gender differences exist is not clear, however it has been postulated that the female hormones may in part be responsible [38,41], and the differences inherent between the sexes may be in part related to the upper airway size [40,42]. The distribution of body fat also has been suggested to play an important role, with the male tending to have upper body obesity and the female predominantly lower body [43,44].

O'Connor et al [45] retrospectively reviewed over 800 patient records looking at the differences in sleep study results, concluding that OSAHS was less severe in women. Reflecting that this was because they tended to have their events mainly in REM sleep, and because of this they may therefore present at a lower AHI as the REM events have more of an impact clinically. These findings were independent of body weight or age, and interestingly they also did not find any significant differences in pre and postmenopausal women.

More recent work has looked at the prevalence of OSAHS in women, it had been previously reported that OSAHS was uncommon in premenopausal women, and increased post menopause [46]. However the data supporting this has been mixed [38,47,48]. Because the relationship with the menopause it has been postulated that hormones have a role in the pathogenesis of this disorder. A recent large study reported a prevalence of 3.3 to 1 male to female ratio; this was in keeping with previous data reported [49]. This study also suggested that HRT was protective in the postmenopausal group. There have also been reports that testosterone is associated with upper airway collapsibility and if given to women it can induce OSAHS, which resolves after the removal of the hormone [48,50]. There is literature suggesting this may in fact be in relation to the effect of progesterone on the upper airway musculature. Other data published has shown differences between the sexes of upper airway fat distribution [42].

Recent work from Sydney has suggested that the prevalence of the disorder is greater than previously thought in the premenopausal group and that the cardiovascular risk for this population is higher that previously reported [51]. It has been postulated that the hormonal changes associated with the menstrual cycle affect ventilatory control, which in turn affects the upper airway dynamics and predisposes to OSAHS.

There is no doubt there are differences in the prevalence of this disorder between the sexes, the reasons for this are complex and multi-factorial, and this is being actively researched.

1.8 Obesity.

The classical Pickwickian patient was described as obese, and there is no doubt that obesity is an aetiological factor for OSAHS in many patients, however not all OSAHS patients are obese. Central obesity, waist-hip ratio and neck circumference are better correlated with indices of OSAHS than BMI per se [52-54], and these tend to be more prominent in men and may in part explain some of the gender differences in prevalence.

Upper airway narrowing is thought in part to be due to fat deposition especially lateral to the upper airway [42,55], along with external compression of walls by the obese neck and heavy jowls. Magnetic resonance imaging (MRI) has been used to show the fatty infiltration into the pharyngeal tissue [55]. Palatal enlargement is also seen with increased fat deposition and increased muscle bulk [56]. The impact of obesity in this patient group cannot be underestimated but there is no doubt that the aetiology is complex, and it has to be remembered that this disorder does not only affect the obese.

1.9 Anatomic Factors.

Retrognathia, micrognathia (congenital or acquired), and retroposition of the mandible all contribute to a reduction in upper airway size. The pharyngeal cross-sectional area also varies with lung volume, increasing as lung volume rises [57]. Tonsillar, uvular or adenoidal hypertrophy can all contribute to obstruction, especially in children. The soft palate when exposed to recurrent vibratory trauma (snoring) and high negative intra-lumenal pressure, this can result in lengthening of

the soft palate secondary to stretching, thickening and oedema. Patients with this condition tended to have a narrower than average retropharynx even when awake although a large overlap exists with normal [58]. The site of narrowing is usually at the level of the tongue and soft palate with two probable contributing factors: fat deposition as previously discussed and a familial tendency for retro-position of the maxilla and mandible [59].

Some medical conditions can also predispose to OSAHS including myxoedema and acromegaly. Congenital disorders such as Pierre-Robin Syndrome, or Treacher-Collins syndrome provide an anatomical predisposition to the syndrome. More subtle craniofacial abnormalities may be evident on cephalometric radiographic studies.

1.9.1 The Upper Airway.

1.9.1.1 The Normal Upper Airway.

Figure 1.3: MRI of the Upper Airway.*

Saggital section:

The upper airway consists of the nasal airway, the oral airway, the pharynx, the larynx and the trachea. The soft tissues and skeletal components comprising these structures determine the upper airway size. The narrowest point of the normal upper airway in the awake horizontal patient, is behind the soft palate, however during sleep the biggest increase in resistance was at the level of the palate in half of patients and the hypopharynx in the remaining half. During normal breathing the nasal airway is responsible for 50% of the respiratory resistance, which is dependent on many other factors including posture. The oral airway can produce significant resistance unless the mouth is wide open. Resistance can be generated in the supraglottic and glottic regions.

Patency is critically dependant on the action of the dilator muscles, stylopharyngeus, salpingopharyngeus, palatopharyngeus and palatoglossus, there may be more muscles involved which contract during each inspiration to prevent upper airway collapse. The muscles of the tongue are critically involved in this process with genioglossus, hypoglossus, styloglossus, chondroglossus all contributing. These upper airway muscles balance with the intra-lumenal pressure to keep the upper airway patent. During inspiration the negative intra-lumenal pressure tends to narrow the upper airway and this is opposed by the action of the upper airway dilating muscles tensing with each inspiration thus resisting collapse of the upper airway. Several mechanisms are involved both functionally and anatomically; the relative importance of each factor varies from one patient to another.

- MRI reproduced from the virtual hospital (www.vh.org).

1.9.1.2 The Upper Airway in OSAHS.

Whether anatomical or physiological factors are the main determinants of upper airway narrowing remains unclear. The level of occlusion varies within individuals, several factors contribute to this; collapse of lateral oropharyngeal walls, relapse of the tongue against the soft palate and the posterior pharyngeal wall and concentric collapse of the hypopharynx. Since OSAHS only occurs during sleep, central nervous system activity has a role in the pathogenesis of upper airway collapse. Narrowing of the pharyngeal airway leads to vibration of the flaccid tissues and generates the noise of snoring.

Patients with OSAHS have a narrower than average airway when awake, but there is a large overlap with the normal population as previously noted [58,60]. Obstruction in the oropharyngeal region is secondary to variable combinations of:

- inward closure of the lateral pharyngeal walls just below the nasopharynx,
- posterior motion of the tongue, downward and posterior movement of the soft palate, closing the velopharyngeal sphincter,
- downward motion of the pharynx secondary to hypotonia and negative pressure,
- with or without an active component of the pharyngeal constrictor muscles.

Upper airway collapse occurs when sub-atmospheric pharyngeal pressure generates during inspiration exceeds the stabilising forces generated by contraction of the dilator and abductor muscles of the upper airway. These muscles are typically activated during inspiration just before diaphragmatic contraction so that by the time

intra airway pressure is negative; the upper airway had been splinted by the muscles to prevent collapse. Mezzanotte and Suratt [61,62] showed increased activation in the tongue muscles during wakefulness, which may reflect the need to keep the upper airway patent.

Some patients with OSAHS generate progressively more vigorous inspiratory events during the apnoeas with oesophageal pressure reading minus 80 to minus 100 cmH_2O. It is this negative intrathoracic pressure, which appears to lead to the arousal from sleep which allows breathing to resume as the upper airway dilator muscle tone returns, but also results in the sleep disturbance and blood pressure changes that lead to the clinical entity of OSAHS. The degree of oxygen desaturation varies from patient to patient, it is not simply related to the number and duration of each obstructive event, it involves other physiological variables, the most important of which seems to be wake oxygen tension and lung volume.

Secondary to hypopnoea or apnoea the patient would be progressively asphyxiated until arousal from sleep occurs. Arousal restores muscle tone in the dilating muscles, the patient gasps or snorts, takes a few breaths and the cycle starts again. These arousals lead to brief awakenings from sleep, secondary to the increased respiratory effort [63]. This can occur hundred's of times per night, resulting in sleep fragmentation, and poor sleep quality.

1.10 Epidemiology.

OSAHS is at one end of a continuum of disorders starting with normal through snoring to OSAHS. Snoring has been reported in up to 60% of adults [64-71], but only a small minority of snorers develop OSAHS.

The prevalence of OSAHS is 1-4% of middle-aged adults [1,72-76], and only a fraction of these patients are as yet diagnosed.

The Wisconsin sleep cohort is a large longitudinal study which is following the natural history of the cardiopulmonary consequences of SDB; from which the estimates of 1-4% of the population having OSAHS have been derived [1]. Partinen and Telakivi [75] quoted the prevalence of OSAHS in adult males to be about 1%, quantifying this further that in the 40-65 year old group it may be as much as 8.5% or more. With ageing populations, looking at SDB in the > 65 year old age group is important. It is generally accepted that in this age group sleep patterns alter. Snoring and SDB are seen with increasing frequency as you increase in age [73,77]. It is not clear why snoring and SBD increase with age, it may reflect a reduction in muscle tone in the upper airways or an increase in body weight. It may also reflect the changes in facial anatomy that occur with age, thinning of the facial bones, loss of teeth and gum tissue. Also there may be an increase in periodic breathing associated with cerebrovascular disease, heart failure and a reduction in the depth of sleep.

1.11 Mortality and Morbidity.

Mortality rates from all causes are increased by 30% during sleep. Morbidity and mortality studies have shown an increased prevalence of disease in patients with

OSAHS. Retrospective studies have shown that OSAHS is associated with an increase in mortality in excess of 30% in some studies [78-81], and an increase in morbidity.

OSAHS may be associated with many medical conditions, for example systemic hypertension [82], pulmonary hypertension [83], cardiac arrhythmia's [84], ischaemic heart disease [78,79] and stroke [85]. Other investigators have compared treated SDB patients and untreated groups with SDB, showing higher mortality in the untreated groups [78,80,86], however one major pitfall of these studies is that they failed to include a randomly selected control sample.

Partinen et al [80] found a significant increase in mortality in their cohort (n = 198) of OSAHS patients and reported that 14 patients died over a five year period. The reported deaths were in the conservatively treated group (n = 127), giving a mortality of 11%, compared to zero in the tracheostomised patients (n = 71). On reviewing the cause of death > 50% were cardiovascular in origin and the majority occurred during sleep. This study was retrospective in design and therefore has to be interpreted with caution. Retrospective studies have also shown the association of OSAHS with increased mortality and morbidity is generally secondary to cerebrovascular and cardiovascular events [78,80]. OSAHS and probably snoring are associated with a poorly understood increase in cardiovascular mortality [87].

The increased risk of road traffic accidents and accidents in the work place have also been reported leading to an increase in mortality and morbidity [88-93], from the sequelae of accidents. The road accidents tended to be of higher impact and have higher mortality and morbidity than with the normal population.

It is clear however that OSAHS needs to be recognised as a significant public health problem, with appropriate education of the medical community and the public as a whole in the recognition of the disorder, taking an appropriate history and ensuring adequate investigation and treatment [94,95].

1.12 Consequences of OSAHS.

1.12.1 Blood Pressure.

Acute rises in pulmonary and systemic arterial pressure occur in association with apnoeic episodes secondary to a complex series of physiological events and this is discussed at length in the next chapter.

1.12.2 Cardiovascular.

In normal subjects heart rate drops during sleep and a marked sinus arrhythmia can be seen in NREM sleep, however in REM sleep the heart rate is more erratic. OSAHS and snoring have been associated with a poorly understood increase in cardiovascular mortality compared with the normal population [79,87,96]. The effects of OSAHS on systemic blood pressure during sleep alone can possibly contribute to this.

The prevalence of conduction abnormalities and arrhythmias in the OSAHS patient is up to 48% [84], with sinus arrest being the commonest recorded, and in some cases it has been suggested that the arrhythmia could be fatal [97]. This study also shows no significant arrhythmia recorded in their patient group after tracheotomy. Bradycardia

can occur with a marked sinus arrhythmia, however conduction defects, tachyarrhythmias including supraventricular and ventricular tachycardias, asystole, premature ventricular ectopics are all reported [98-101]. The tachyarrhythmias usually occur at apnoea termination, possibly as a result of the withdrawal of vagal tone, increasing sympathetic tone, hypoxia or acidosis. The clinical significance of these arrhythmias – other than as a marker for apnoeic events – remains to be proven.

Many cardiac deaths tend to occur in the early morning just before and after waking from sleep, there is some evidence to suggest a relationship between OSAHS and these deaths. A higher prevalence of myocardial infarction (MI) has been reported in OSAHS patients compared to the normal population [102-106] but there are many possible confounders inadequately excluded in these studies including obesity, smoking, gender and hypertension. A case controlled study looking at 50 patients with recent MI showed that snoring was an independent risk factor with an odds ratio of 4.4, however no PSG was performed and it was self reported snoring [107], however it provides an interesting area for further research.

1.12.3 Cerebrovascular.

Studies have been done, to determine whether OSAHS is a risk factor for stroke [85] and if stroke predisposes to OSAHS [64,108-111]. Partinen reported a case controlled study [109], which looked at men with strokes comparing them with age-matched controls. He reported the risk ratio (RR) of stroke at 10.3 in patients who snored compared to non-snorers. Koskenuo [64] also reported data from a large prospective epidemiological study, of the 42 patients who had strokes; the odds ratio (OR) of snorers against non-

snorers was 1.4. Spriggs [110] concluded that snoring was a risk factor for stroke in both sexes and all age groups, also the greater the snoring the greater the risk.

Large population studies carried out in the 1980's have shown that diastolic blood pressure (DBP) is partially related to stroke, not just in the 'hypertensive' but in the 'normotensive' subjects [112,113]. Significant relationships between DBP and stroke risk continue with no lower 'threshold' for a reduction in DBP that is not associated with a reduction in stroke risk.

Impairment of the cerebral blood flow autoregulation has been postulated as a possible mechanism for the genesis of stroke [114,115], this is thought to be affected by the cyclical swings in blood pressure. Palomäki reported that snoring may be a risk factor for ischaemic stroke as there is a higher prevalence of stroke in snorers than non snorers [85]. The OR of snoring for ischaemic stroke was calculated to be 2.13, and in patients with OSAHS this increased to an OR ratio of 8.0. Dyken et al [111] reported that patients with recent stroke have an increased incidence of irregular breathing during sleep compared to matched controls. However this was a small group of patients (n = 24), reporting a 21% mortality at 4 years, and all the patients who died had co-existing irregular breathing. The likeliest time for the occurrence of ischaemic stroke is during sleep and in the first hour of wakefulness [116]. This could be related to the surges in the blood pressure associated with arousal, or associated with the arrhythmias described. Palomäki [105,117,118] also concluded that there was an increased vascular morbidity in OSAHS although the mechanisms were poorly understood however sympathetic activation, platelet aggregation and catecholamine release have all been postulated [119].

These studies suggest there is an increased cerebrovascular risk from snoring itself and OSAHS, but whether this is independent of confounders is unclear and the possible mechanisms require further consideration.

1.12.4 Renal Function.

The effect of OSAHS on the kidney is unclear, it is exposed to the cardiovascular and arterial blood gas tension changes occurring as a consequence of the apnoeas and hypopnoeas. There have been case reports of the effect of OSAHS on the kidney [120,121] and studies performed in an attempt to clarify this relationship further [122-126].

Bailey [120] reported a morbidly obese man with OSAHS who developed a glomerulomegaly and focal glomerulosclerosis, the authors attributed this to his obesity, however the diagnosis of OSAHS was not considered and perhaps played a role in the aetiology of the renal disease. A further case report [121] of a morbidly obese man with associated OSAHS who developed a focal segmental glomerulosclerosis; the patient went on to have a tracheostomy to treat his OSAHS. The authors postulated that the OSAHS had an aetiological role in the development of the renal disease.

Sklar et al [122] studied 9 healthy controls, 12 obese patients (with normal PSG) and 14 OSAHS patients. The authors studied nocturnal urinary protein excretion in these groups, reporting that levels were commonly elevated in OSAHS patients. The authors tried to control for confounders and attempted to match the control group, however this group was younger, lighter and had slightly lower BP, the authors did not comment whether these differences were significant.

Fletcher reported a study of patients attending a renal dialysis centre recruiting patients who complained of symptoms of OSAHS [123]. He reported a prevalence of OSAHS of 73% in patients he studied. However a control group was not included and patients with renal disease can have many of the same symptoms of OSAHS, it was not clear how and when these patients were studied.

Chaudhary [126] reported the results of dipstick urinalysis in 34 patients attending for sleep study matching them to a control population, and showed that 18% of the OSAHS had ≥ 3+ proteinuria on stix testing, defined as high grade proteinuria (3 g/l), compared to none in the control group. Interestingly the proteinuria was shown to improve after treatment for OSAHS was commenced. A further study was performed by Chaudhary et al [124] who analysed urine from 407 patients attending a sleep centre with known OSAHS (AHI > 15), performing dipstick testing. They concluded that severe proteinuria in OSAHS occurs in patients with a higher AHI, the lesser degree of proteinuria cannot be explained by AHI alone.

Iliescu et al recently reported that clinically significant proteinuria was uncommon in OSAHS [127]. They recruited 224 patients who were referred to their sleep centre, performing overnight PSG and measuring their urinary protein to creatinine ratio. OSAHS was diagnosed (AHI ≥ 5 hour/slept) in 63.8% of this cohort. They reported that AHI and urinary protein were weakly correlated, which was related more to the degree of hypoxaemia than to the frequency of apnoeic events. They did not include a normal population using the patients who had normal sleep studies as their controls, however these patients were not matched and must have been symptomatic as they were attending the sleep centre.

Thus there is evidence that patients with OSAHS have co-existing renal functional abnormality, however what the aetiology and significance of this is unclear and requires further investigation.

1.12.5 Excessive Daytime Sleepiness.

Excessive daytime sleepiness (EDS) is the feeling of being abnormally sleepy in wake time. EDS is not specific for OSAHS and occurs in a variety of conditions. It may also be underreported as many patients lose their frame of reference for what constitutes normal sleepiness. Sleep restriction or sleep fragmentation from any cause produces daytime somnolence [128,129].

Improvements in the Epworth sleepiness score (ESS) in patients with OSAHS after treatment have been shown [130,131], and is further discussed in section 3.2.1. The ESS is a useful subjective method of following up patients on treatment and has been shown to correlate with the frequency of apnoea in OSAHS [132]. Objective improvements in sleepiness have been proven after treatment with CPAP in this patient group [133]. More objective evidence has been provided using the multiple sleep latency test (MSLT) and the maintenance of wakefulness test (MWT), showing improved times after treatment with CPAP [134].

1.12.6 Cognitive Function.

OSAHS can also cause cognitive impairment with deficits in thinking, perception, memory and communication. There are neuropsychological deficits in OSAHS, which improve with nasal CPAP treatment [4,133,135-140]. There are randomised controlled

trials [133,135,136,139,140] included in this group of studies giving a good evidence base for the data, both using an oral placebo and 'sham CPAP'. Function is assessed using tests of vigilance, mental flexibility and attention. Some of the data suggests that the degree of hypoxia is a better correlate of the dysfunction rather than AHI [4,141,142].

More sophisticated neuropsychological studies have been done [143], showing impaired ability to initiate new mental processes, reduced memory spans, and a tendency for perseverative errors. These studies have tried to focus cognitive tests in an attempt to try and pinpoint the disabilities more clearly. There has been some concern that some of the effects of OSAHS are irreversible possibly secondary to anoxic damage within the central nervous system [144].

1.12.7 Quality of Life.

Quality of life (QoL), is frequently assessed in patients with a variety of disorders. It is a measure of total well-being, which includes both physical and psychosocial factors. Functional status is an important component of QoL, and is defined as a 'multifaceted concept that characterises the ability to meet needs, fulfil roles, and maintain health and well-being' [94]. Changes in functional status can be secondary to many different factors including mood, motivation and a variety of medical conditions.

Sleepiness is a difficult symptom to quantify and its complex effects on day to day living can be difficult to realise. Scales of sleepiness have been used for many years, but they only give insight into how sleepy individuals are in specified situations but do not reflect the impact of sleepiness on their normal life. Sleep specific sleep

questionnaires have been employed to look at the impact of sleepiness in day-to-day life. Several questionnaires have been developed, including the functional outcome of sleep questionnaire (FOSQ) [145], Calgary sleep apnoea quality of life index (SAQLI) [146], Sleep and Heath Questionnaire [147] and the Berlin Questionnaire [148]. These questionnaires compliment the general quality of life questionnaires frequently used e.g. Medical Outcomes Short Form-36 (SF-36) [149,150] and the Nottingham health questionnaire [151,152]. These questionnaires have been used to show that the outcome measures improve in OSAHS patients with treatment in both randomised controlled trials [133,136,140,153] and non-controlled studies [137,141,154-159].

OSAHS not only affects the patient, their partner also suffers from the snoring, which disrupts and fragments their sleep, and from the patient's restlessness with limb movements, especially at the time of arousal. One study tried to quantify this effect formally. In the setting of a randomised controlled trial, patients and their partners were studied in their own home at the end of a month treatment limb, comparing CPAP with an oral placebo. They reported that partners had poor sleep quality and self reported health status, however only subjective sleep quality benefited from treatment of the patient with CPAP [160].

1.12.8 Accidents.

In patients with OSAHS there is an increased risk of road traffic accidents, and probably also accidents in the home and industrial incidents. There is considerable evidence that sleepiness is a major contributing factor to road traffic accidents, and accidents are more frequent in OSAHS than the general population [88-91,93,161-167]. Recent

data has suggested that to identify the patients more at risk of accidents it is better to identify the patient by direct questioning who is a sleepy driver rather than just generally sleepy. This in turn is a better predictor of identifying the group of patients with SDB, and hopefully allows early intervention to prevent accidents [167].

Studies using driving simulators, in an attempt to assess a patients fitness to drive and as a method of assessing vigilance have shown that patients with OSAHS perform poorly on these tasks [168-173] and worse than matched normal subjects made legally drunk [170].

There is data in OSAHS patients suggesting a 2-7 fold increased risk of road traffic accidents, according to Findlay et al [90,174]. There were more single vehicle accidents with increased fatalities compared to the normal population, the accidents tended to be of higher impact and therefore more serious [175]. One in three patients with untreated OSAHS will have an accident in a 5-year period [176]. It had been shown by Engleman et al that self reported accidents reduce significantly with CPAP treatment in patients with OSAHS, compared to an untreated group, this was reinforced with objective data [92,177].

Suratt et al in an editorial [178] stressed the need for increased awareness of this disorder by the population as a whole and its impact on driving and accidents in general. McNicholas echoed Suratt's concerns on behalf of a working party looking at the impact of sleep disorders on driving [179]. The cost implications of accidents is huge both financially and in terms of mortality and morbidity [180-183].

1.13 Upper Airways Resistance Syndrome.

Upper airway resistance syndrome (UARS), refers to a group of patients who are generally non obese who have increased respiratory efforts terminated by transient alpha EEG arousals, but who do not have the associated upper airway collapse, hypoventilation or reduction in oxygen tension. If oesophageal manometry is performed it shows the increased respiratory efforts made that precede the arousal. These transient arousals would normally be ignored in sleep study analysis, but it is enough to fragment sleep, their impact was evident with increased sleepiness in the daytime shown objectively on the MSLT [184].

In UARS there seems to be a lower arousal threshold compared to the OSAHS patient. UARS may also cause the same clinical picture as OSAHS. There remains much debate about whether UARS is a separate clinical entity or just forms part of the spectrum of OSAHS and snoring. A recent editorial debate on UARS between Douglas and Guilleminault has discussed this further [185]. Guilleminault postulated that UARS patients have intact mechanoreceptor function whilst in OSAHS this was blunted. This in turn affects the central nervous system response to the insult, as the receptor reflexes are so different. Douglas comments on the evidence that UARS has no signs on examination and the symptoms are the same as for OSAHS. Furthermore that the diagnostic criteria do not fulfil the original description, and there remains debate over the scoring of sleep studies especially with hypopnoeas. It may just reflect the use of inadequate sensors in sleep studies rather than a different disease entity. The diagnostic criteria set out fall within normal limits, and oesophageal manometry is not often performed as it is unpleasant for many patients

and falls in pressure may reflect increased ventilation rather than increased resistance per se. A major concern is that patients may be labelled with this 'diagnosis' and an underlying problem missed. Clearly more work needs to be done in this area to clarify this difficult diagnostic group of patients.

1.14 Clinical Presentation.

OSAHS is a chronic disorder, which develops with an insidious onset, with alterations in airway patency, modifications in ventilation, quantity and quality of sleep, and frequency of sleep disruption. OSAHS is a prevalent disorder and it is important to keep a high index of suspicion and ensure pertinent questions are asked in the appropriate clinical setting. Many patients present with vague symptoms, including general fatigue and impaired concentration. There is a very wide spectrum of symptoms from the minimally affected to the classical Pickwickian subject, it is not clear why some patients who have mild disease have many symptoms and some with severe disease have relatively few.

Loud snoring is present and associated with snorting and silences during which the apnoeas occur. These may be witnessed by the bed partner and family, and can be alarming. Abnormal behaviour during sleep is occasionally seen with abnormal movements ranging from mild twitching to more generalised motor activity. Enuresis is relatively common. Morning headache can occur, and is usually frontal but can be diffuse, tending to resolve 1-2 hours following rising. The pathophysiology of the headache is unclear, however it is thought to be linked to

cerebral vasodilatation overnight, and possibly CO_2 has a role. A reduction in sexual drive is often reported secondary to fatigue with occasional impotence.

Daytime somnolence is frequently the reason for referral to a sleep specialist, with extreme drowsiness in inappropriate situations, and an undeniable urge to sleep, which is especially hazardous whilst driving. Patients commonly complain of nocturnal choking, frequent awakenings overnight, and unrefreshing sleep. They often feel like they have not slept well, and suffer from poor concentration during the daytime.

Clinical examination often reveals very little, obesity is common, facial abnormalities can be obvious however more subtle abnormalities can be more evident with the use of cephalometric studies [186,187]. Blood pressure should be checked, as it is reported that in 60% of adults with this disorder there may be associated elevations in systolic and diastolic blood pressure [82,188-191]. Chest wall abnormalities are usually evident.

Neck circumference should be recorded, in men it is often recorded as collar size, as there is a correlation with neck size and severity of disease [44,53,192,193]. Examination of the nose can reveal blocked nasal passages, which could contribute to the problem. Examination of the mouth reveals any crowding of the oropharynx due to tonsillar hypertrophy, oedema or a narrow retropharyngeal space. Evidence of cor pulmonale should also be sought, suggesting either underlying pulmonary disease or perhaps decompensated pulmonary hypertension.

The differential diagnosis includes other sleep disorders such as UARS, narcolepsy, periodic limb movement's (PLM's), and a variety of medical conditions including depression and diabetes. This disorder is generally under recognised [194,195] because of

its vague symptoms, the lack of pertinent history taking and the lack of any specific clinical signs.

1.15 Diagnosis and Investigation.

The diagnosis is made from investigation, focused history taking can be suggestive, however sleep studies require to be performed to establish a formal diagnosis. Using arterial oximetry alone misses about one third of cases [196], the 'gold standard' investigation being polysomnography (PSG). However PSG has not been particularly well validated, although many studies and other mechanisms of sleep study are referenced to it.

With a suggestive history the next step is to perform a sleep study either using a limited system in the home or hospital setting, or using full in laboratory PSG. PSG consists of a multi-channel recording of electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), airflow, respiratory effort, body position and motion sensor, and arterial oxygenation saturation, the data is stored via a computer system (*System S*, Compumedics, Melbourne, Australia). There is a continuum from normal through snoring to disease, and somewhere along this line the patient become symptomatic. The point at which this occurs appears to vary markedly between individuals.

1.16 Treatment of OSAHS.

1.16.1 Behavioural.

In some patients OSAHS is related to the supine position, therefore it was hoped that by preventing the subject from being in this position the problem would be cured. However this has rarely been successful. Ensuring adequate sleep time is important in this group of patients, so called 'sleep hygiene', as insufficient time in bed will add to daytime somnolence. Avoidance of any aggravating factors is also helpful but rarely cures, such as the avoidance of sedative medication and alcohol especially before bedtime. Weight loss is recommended for the obese but adequate weight loss to cure OSAHS is rarely achieved [197]. Exercise is recommended which can aid weight loss but also may have effects on sleep architecture.

A Cochrane review has been done looking at lifestyle modifications in the treatment of OSAHS [198], at the time of review no published randomised controlled trials were identified. Concluding that there is a need for lifestyle studies to be done allowing identification of the subgroups of patients would benefit from these interventions.

1.16.2 Medical Therapy.

1.16.2.1 Drugs.

A pharmacological solution to OSAHS would be very useful, it would be much more acceptable to patients than CPAP, easier to transport and less obtrusive in the bedroom. Different agents have been tried in the past [199].

Oxygen therapy can increase the duration of the apnoeas and is therefore not recommended [200-202].

Progesterone has been used in the past as a respiratory stimulant but there is no RCT evidence of clinical efficacy in OSAHS [38,203]. It is a respiratory stimulant, and it was postulated that it would increase respiratory drive and in doing so it would increase pharayngeal tone. However no improvements were seen in the small studies performed [199,203].

Acetazolamide causes a metabolic acidosis and it was postulated that this would improve SDB. A randomised double-blind placebo controlled crossover study by Whyte et al showed a reduction in the frequency of apnoeas, however the apnoeas were predominately central in origin [204], with little work being done looking at OSAHS as such, however there is no evidence of efficacy in OSAHS [205].

Protryptyline has been shown to reduce apnoea index and desaturation by reducing the amount of REM sleep, as the OSAHS tends to be more severe during REM sleep, daytime hypersomnolence was also improved in these studies [206-209]. It was though it could be useful in up to 50% of patients however its use was limited by side effects, and has no place in the modern treatment of this disorder [63].

Sabeluzole is a putative glutamate antagonist and has been used in a small double-blind crossover study (n = 13). Results suggested that Sabeluzole reduced the desaturation index in OSAHS patients [210]. Further research needs to be done with this drug.

Modafinil is a new wake-promoting agent used in the treatment of Narcolepsy, some trials have been done in patients with OSAHS to see if it is of benefit. A randomised-controlled trial has been performed looking to see if modafinil is a useful

adjunct for the OSAHS patient who continued to be sleepy despite adequate CPAP use. It demonstrated that modafinil did improve alertness significantly; interestingly it also reduced CPAP use [211,212]. More work is being done in this area.

Serotonin has been more recently suggested as a possible pharmacologic agent in the treatment of OSAHS [213]. Serotonin is a neurotransmitter; it has been implicated as a contributor to the disorder but more recently suggested as a possible therapy. Selective serotonin reuptake inhibitors (e.g. Fluoxetine) have shown moderate decreases in AHI in NREM sleep but the clinical efficacy is unproven and likely to be low.

1.16.2.2 Intra Oral Devices.

Intra oral devices (IOD) are often used as an alternative to CPAP therapy in patients with mild disease and those intolerant of CPAP. There are more than 40 different designs available. The devices are also referred to as mandibular advancement devices (MAD) or mandibular repositioning splint (MRS). Common side effects include excess salivation, mucosal dryness, tooth discomfort and temporo-mandibular joint discomfort [214].

These devices have been developed as an aid for snoring and for the treatment of OSAHS. CPAP therapy although a good treatment, has major drawbacks (which are discussed further in Chapter 10), this has fuelled the search for other methods of treatment which would be more acceptable to the patient.

Many different devices are available and they vary in size, cost, ease of manufacture, and 'shelf life'. Most require custom fitting and adjustment ideally by a well-trained

individual. They generally have a 'shelf life' of approximately 6 months, then require to be replaced. Recent evidence suggests that although for some they work well, with around 50 % of patients' breathing normalised, this however leaves 50% of patients who are not or only partially treated [215]. It has been shown in a RCT that IOD's are effective in the management of snoring [216]. Several studies have suggested MRS as a first line choice for mild to moderate OSAHS patients [215,217-221] but this has been challenged [222]. Comparisons between MRS and CPAP report that MRS is an effective treatment in some mild to moderate OSAHS patients, and was associated with fewer side effects and has greater patient satisfaction that CPAP [220] although others have found CPAP to be associated with better outcomes across all OSAHS severity's [222].

Further data has been produced comparing 2 different types of MRS, a one-piece device against a two piece device. Patients were recruited who had been unable to tolerate CPAP for a variety of reasons, introducing bias. Patients tried both devices and had no treatment, in a random order for a period of a week each, with satisfaction questionnaires and sleep studies performed at the end of each treatment period. The results show that one device is preferred (the simpler one), over the other producing better relief of symptoms, however both devices were effective treatments for OSAHS [223].

A recent randomised controlled trial compared a MRS with a placebo MRS plate by performing PSG to document the effects on sleep quality. Data showed that the MRS was better than placebo in terms of sleep quality [221,224]. Therefore it is important to chose a device to suit a patients needs, and to select the patients for this treatment.

More work needs to be done on patient selection, and on the importance of the differences between the devices available.

Tongue retaining devices are seldom used, as they may be uncomfortable to wear [225]. They comprise a custom made device which fits over both dental arches with an attachment between designed to hold the tongue in a forward position.

1.16.2.3 Continuous Positive Airway Pressure.

Continuous positive airway pressure (CPAP) is the standard proven treatment for OSAHS [226,227]. CPAP is delivered by a small portable flow generator. There are several different makes available, varying in design, size and cost. The principle is that they will deliver a positive pressure to the upper airway providing a pneumatic splint, stopping the airway collapsing and therefore preventing apnoeas and the subsequent arousal. The pressure is applied via a close fitting nasal or oro-nasal mask. Sullivan et al were the first group to use CPAP in this group of patients and published their results in 1981 [228]. They demonstrated virtual abolition of apnoeas and oxygen desaturations with resultant improvement in daytime symptoms, and abolition of snoring.

The side effects of CPAP are usually minor and include discomfort from the mask, nasal congestion or dryness and occasionally rhinorrhoea. The concept of wearing such a device every night is not attractive, however most patients feel so much better using it, they put up with the inconvenience of wearing the mask. The use of CPAP in the first 3 months is a good predictor for long-term use [229]. It has also been shown that intensive initial support with education for the patient and partner improves

CPAP use [230-232]. CPAP can undoubtedly stop the arousal from sleep caused by the obstruction in the upper airway [228,233-236]. Treatment with CPAP allows normal sleep architecture to return and the phenomenon of REM rebound is frequently seen, however it is short lived [237].

Less subjective sleepiness is reported in patients treated with CPAP [131,236], and patients are also less sleepy on objective testing [135,136,238]. Improvements in quality of life are also shown using subjective questionnaires [145,159,239,240]. The question whether this is all a placebo effect has been posed, however prudent use of randomised controlled trials have shown that CPAP is better than placebo in these patients.

Wright and colleagues [241] questioned the efficacy of CPAP in 1997, when they concluded that there was little evidence to suggest that CPAP was beneficial in these patients. However the argument was unbalanced; examining mainly the effects on cardiovascular disease, not on the cognitive effects, improvements in quality of life, and improvements in driving performance, which had been documented, albeit at that time only in one adequately controlled study [242].

A consensus statement was published from the American Sleep Disorders Association listing the indications for CPAP therapy [243]. They concluded that CPAP was indicated for all patients with OSAHS with an RDI $\geq$ 30 events per hour slept, irrespective of symptoms because of the cardiovascular risk evident from the Wisconsin Sleep cohort. However that statement is not based on any adequate therapeutic trials, it is derived from population studies. For Patients with an RDI between 5 and 30 events per hour slept CPAP is indicated on the grounds of clinical symptoms and patient co-morbidity. It is not recommended for asymptomatic patients with no cardiovascular disease [243]. These guidelines have not been accepted

practice in most UK centres, partly because it would be difficult to convince an asymptomatic patient to comply with therapy, but much more importantly the evidence is lacking [244].

A Cochrane review has also been performed looking at CPAP treatment for OSAHS [245]. The conclusions were that CPAP appeared to be more effective than placebo in improving health status, that it was better at reducing the respiratory disturbances than MRS devices. Patients preferred MRS over CPAP, but chose CPAP over placebo.

There is no doubt the CPAP is an effective treatment for OSAHS and the level of evidence is high, the effectiveness of intervention on cardiovascular and cerebrovascular events is still emerging. At present CPAP remains the treatment of choice for the majority of patients with OSAHS.

1.16.3 Surgical Treatments.

It would seem simple that if the problem in OSAHS is due to an unfavourable configuration of the pharyngeal airway, that there should be a simple surgical solution. However although several operative procedures have been tried [246] none are panaceas. Options of removing soft tissues and modification of the underlying craniofacial skeleton have been explored. There is no doubt that surgical procedures can be useful in the minority of patients who have major craniofacial abnormalities. The difficulty in performing any form of randomised controlled trial with irreversible surgical treatments to provide good evidence remains a problem.

Cochrane has once again published a document on the role of surgery in OSAHS [247], they found no published randomised-controlled trials in this area.

1.16.3.1 Tracheostomy.

Tracheostomy bypasses all the sites of obstruction, and is a very effective treatment as shown by Guilleminault et al [248], it is however a very drastic measure, and is rarely used as a treatment for OSAHS now. It brings with it all the associated problems of a tracheostomy, with the requirements of continued care and major psychosocial problems for the patients.

1.16.3.2 Maxillofacial Surgery.

Micrognathia and retrognathia may require mandibular osteotomy and reconstruction [249-251]. Maxillo-mandibular osteotomy (MMO) comprises a combined Lefat 1 osteotomy and advancement of the maxilla and mandible [252,253]. Other complex maxillofacial surgery could be considered in a small number of specialised cases with procedures such as genioglossal advancement with or without resuspension of the hyoid bone, with or without uvulopalatopharyngoplasty (U3P). It is impossible to perform a large scale randomised-controlled trial in this group of patients, as the surgery is major and would only be considered in a minority of patients. However MMO seems to be as effective as CPAP [253], and at 2 year follow up in a small group of patients (n = 15) who had maxillo-mandibular advancement, treatment has been shown to remain effective [253].

1.16.3.3 ENT Surgery.

If nasal obstruction is present it should be corrected. This may reduce the noise of snoring by reducing turbulence of airflow, however it does not however cure OSAHS [254]. There is no good evidence that it will make therapy with CPAP easier. Removal of enlarged tonsils or adenoids can be effective in children, and occasionally in adults.

1.16.3.4 Uvulopalatopharyngoplasty.

The uvulopalatopharyngoplasty (U3P) procedure widens the pharynx by a combination of tonsillectomy, removal of the redundant mucosa and soft tissue of the uvula, soft palate, posterior pharyngeal walls and posterior pillars [251]. Initial studies reported a 50% reduction in apnoea frequency but not a cure. The surgery is painful, often unsuccessful and it makes treating the underlying OSAHS a little more difficult with conventional means. The surgery is associated with complications including velopharyngeal insufficiency, voice change, post-operative bleeding, nasopharyngeal stenosis and a foreign body sensation.

Meta analyses of short-term (< 6 months) outcomes of this procedure have shown a 50% reduction in AHI, however this procedure did not cure OSAHS [78,207,255,256]. A further study reported that the U3P is not effective in patients with severe OSAHS [257]. A major concern with this operation is that it may well reduce the noise of snoring but it does not treat the apnoeas and so patients continue to have these events associated with all the physiological changes and sequelae. Patients who have had a

U3P also poorly tolerate nasal CPAP [258] and tend to require full facemask if commenced on CPAP.

1.16.3.5 Laser Assisted Pharyingoplasty.

The laser assisted pharyingoplasty (LAUP) operation may be of benefit in snoring but there is little convincing evidence that it is useful in patients with OSAHS with little pre and postoperative sleep data being available. It enlarges the retro-palatal airway by ablation of the uvula and the posterior margin of the soft palate using a carbon dioxide laser. It can be performed under local anaesthetic [257,259,260].

1.16.3.6 Laser Midline Glossectomy.

Laser midline glossectomy (LMG) or lingaplasty involves the central portion of the tongue being excised with a laser reducing the muscle mass, enlarging the retrolingual airway [251]. There are no randomised-controlled trials available in the treatment of OSAHS with this procedure.

1.16.3.7 Somnoplasty.

This procedure consists of radio-frequency ablation of the palate and tongue base [250,261]. An animal model has been developed which shows the reduction in tongue volume with this technique, inferring that it might be a useful technique for OSAHS. This needs to be followed up with a randomised-controlled study looking at its use in OSAHS.

1.16.3.8 Diaphragmatic Pacing.

Diaphragmatic pacing was used very occasionally for pure central sleep apnoea; it was however limited by the development of pacing induced upper airway collapse [262,263]. It is used very occasionally in the treatment of children with congenital central sleep apnoea (Ondine's curse). There are also case reports of using pacing in the upper airway to offset the upper airway collapse in OSAHS with variable results. There is no RCT evidence in this area [262,264,265].

1.17 Discussion.

OSAHS is a complex multi-factorial disorder that has wide reaching implications many of which are as yet not fully understood. Although CPAP is the treatment of choice not all patients are able to tolerate it, IOD's may be useful in many 'milder' patients, but have their own associated problems. The surgical options are varied but only MMO has a real evidence base supporting it. It is also evident that the current treatments available are not ideal, and further research needs to be done to find a better treatment that would be acceptable to all, and in the long term ideally to find a cure.

Chapter 2.

Blood Pressure and Sleep.

2.1 Introduction.

Blood pressure (BP) is a biological characteristic of an individual, with wide inter-individual and intra-individual variability. The distribution curve of BP is slightly skewed to the right. The spread of values reflects the influence of genetic, racial, social and environmental factors, which are inter-dependent factors. BP tends to be higher in social class 4 and 5, with diet, alcohol, exercise, ethnic origin, and possibly stress all differing between social classes. In western societies a gradual rise in the systolic blood pressure is seen until the seventh decade in men and the sixth decade in women. However diastolic blood pressure rises in both sexes until the sixth decade after which it begins to fall [266].

BP changes over the twenty-four hour period, reaching its nadir in the early hours of the morning and its maximum on rising [266-269]. This is not an endogenous circadian rhythm and is clearly dependent on environmental factors, as diurnal rhythm is not observed in an immobilised patient, or one with autonomic dysfunction (e.g. diabetic), or after cardiac transplantation. Rapid changes in BP can be observed with exposure to pain, mental stress, and exercise. With the onset of sleep, BP gradually falls with the deepening stages of sleep, and remains relatively stable. However in REM sleep the BP is more erratic and is higher than in the other stages but does not usually reach the levels of wakefulness [267].

The nocturnal drop in BP is often called "dipping", it is defined as a nocturnal drop in blood pressure of > 10% of daytime values. The lack of this nocturnal drop in BP (non-dipping) is thought to be a marker for hypertensive disease and in some patients it seems to be associated with a poorer prognosis, acting as an independent predictor of hypertensive end organ damage [270-272].

Several humoral mechanisms influence BP, including the kallokreinin-kinin system, prostaglandins, atrial natriuretic peptide and the reno-medullary lipids. The renin-angiotensin-aldosterone system has an important role to play with salt and water homeostasis, which in turn can influence BP.

2.1.1 Pulmonary Artery Pressure.

The pulmonary vascular bed has its own homeostatic regulations keeping the pressure within its area at necessary levels, and can be affected by a variety of cardiac and pulmonary diseases. Pulmonary arterial hypertension is not uncommon in OSAHS, and may be related to the severity of the obesity and its resultant effects on the respiratory system [273]. These mechanisms are out with the remit of this thesis and will not be discussed further in detail.

2.1.2 Systemic Blood Pressure and Hypertension.

The World Heath Organisation defines hypertension as a BP of > 140/90 mmHg and suggests a threshold for drug treatment at 160/95 mmHg. The target treated BP is < 140/90 mmHg, with lower limits set in the diabetic population. It is important not to take a single reading as diagnostic of hypertension, remembering the effect of the

'white coat'. Recent advances in technology have allowed the development of ambulatory devices to provide BP recordings over a 24-hour period, giving an average reading for the period, and providing more accurate and reliable results.

Systemic hypertension is common and is one of the strongest predictors of cardiovascular morbidity and mortality, including myocardial infarction, heart failure and cerebrovascular disease. Hypertensive disease represents a significant public health problem, and in 95% of cases no obvious cause can be found. It represents a spectrum of disease from mild to severe cases.

The genesis of hypertension is complex, involving physiological dysfunction in the nervous system including the autonomic nervous system, affecting the endocrine system and alterations in cardiovascular function. These interrelated mechanisms augment, stimulate and oppose each other producing a multi-factorial disease. Increasing vascular resistance is the basic abnormality in chronic stable hypertension. Underlying this seems to be two basic mechanisms; a vascular defect leading to enhancement of vasoconstriction and an increase in sympathetic tone. Either of these parameters can be genetically driven or acquired [274]. There is conjecture that initiation of hypertension by one mechanism may trigger off a cascade of events, which may not all be fully reversible if you remove the initial stimulus.

In normal subjects the BP falls during sleep by up to 20%, increasing once more on wakening. During NREM sleep in normal subjects SBP is reduced although this is not a constant drop nor smooth, it contains small oscillations occurring in 20-30 second cycles. The BP is elevated in REM compared to NREM periods, however it does not normally reach the waking levels [275]. This pattern has been shown to be

absent in some patients with OSAHS i.e. non-dipping as previously discussed [276] in section 2.1.

2.2 Genetics.

Hypertension studies suggest genetic mechanisms are one of several factors influencing blood pressure and that they are diluted by various environmental factors. There are some phenotypic associations with hypertension that may provide a clue about some of the underlying genetics. Family studies have shown the importance of some relatively rare single gene defects in familial hypertension. At least four or five genes may be involved in blood pressure control and probably this is an underestimate. Most of the relevant genes have still to be identified [277-279].

2.3 Environmental Influences.

There are many and varied environmental influences on BP, some of which are anecdotal and others have been proven with studies. Nutritionally several components alter BP, suggesting a role for dietary manipulation of BP. However in practice this is not very effective. A reduction in sodium, alcohol and protein intake are associated with a lower SBP [280]. Potassium intake is associated with lower SBP and DBP levels, alcohol (in moderation) is also associated with a lower DBP [280]. The age changes in SBP are attenuated by increased calcium and protein intakes [280]. A reduction in calcium and magnesium intake has also been studied with conflicting results [280,281].

Central obesity correlates better with BP than body mass per se [282], and this is most commonly recorded by looking at the waist to hip ratio [282]. Obesity alone does not increase sympathetic activity [283], however there was a suggestion that dietary weight reduction may be associated with a reduction in sympathetic activity [284], which in itself can reduce BP. Further studies are needed.

Ingestion of more than 6 units of alcohol a day has been shown to be associated with an increase in blood pressure. The lowest BP being associated with 1-2 units of alcohol per day [280] and anecdotally red wine might be more protective.

Vegetarians tend to have a lower BP [266] however the reason for this is unknown, although much postulation has been done. Stress acutely increases BP; whether chronic stress itself leads to sustained BP elevation is still unclear.

2.4 Endothelium and Endothelin.

2.4.1 Endothelium.

The vascular endothelium is a cardiovascular endocrine organ with an approximate surface area of 400m^2, which provides the strategic interface between the blood and the body. It has many regulatory roles, including the modulation of immunoresponses, regulation of vascular cell growth, vasomotor control, pro and anti thrombotic mechanisms, metabolic and immunological functions. It modulates vascular tone with the release of vasoactive substances e.g. prostanoids, endothelin and nitric oxide. It is sensitive to specific growth factors e.g. vascular endothelin growth factor (VEGF), these growth factors are secreted by cells in response to

ischaemia and hypoxia and act via receptors expressed on the endothelial cells [285,286]. This increases vascular permeability, endothelial cell growth, cell proliferation, cell mobility, angiogenesis and vasodilatation [286-290].

2.4.2 Endothelins.

Endothelins are a family of potent vasoconstrictor peptides containing 21 amino acids that are closely related to snake venom toxin. There are three isoforms named 1,2 and 3, and at least two receptors had been identified in human blood vessels, named A and B. They are produced by a wide variety of cells.

Endothelin-1 (ET-1) is synthesised from 'big endothelin' within human vascular endothelial cells. It had a potent and lasting vasoconstriction action on human blood vessels, with an associated increase in blood pressure. However it can also produce transient vasodilatation. In addition to its pressor and vasoconstrictor effects it has been shown to be positively inotropic, mitogenic and to have an anti-natriuretic action. ET-1 also increases central and peripheral sympathetic activity. Stimuli for its release seems to be under the influence of chemical or physical stimuli including hypoxia and thrombosis and by means of various receptor operated mechanisms e.g. tissue growth factor β (TGFβ).

Levels have been shown to be increased in hypertensives, and in patient's with pulmonary hypertension, and it has been postulated they might be elevated in patient's with OSAHS perhaps contributing to elevation of BP seen in this patient group [291], however the relationship remains poorly understood. There is some early data providing conflicting evidence showing no increase in the ET-1 levels in

patients with OSAHS [292], and elevated levels in other studies [291,293]. These studies were small and may have been underpowered. A matched control group is included in some [291,293], but others did not [292]. The studies included hypertensive patients in their study groups, which may have confounded their data.

2.5 Atherogenesis.

Atherogenesis is the formation of atheroma within vessel walls. In the earliest stages of atherogenesis, damaged endothelial cells become dysfunctional, resulting in the formation of plaques. These plaques could then produce growth factors, cytokines, chemo-attractants, clotting factors and adhesion molecules. Monocytes transform into macrophages, recruitment and proliferation of smooth muscle cells occur, which in turn activates the thrombotic process, altering vascular resistance. Within resistance vessels, the wall to lumen ratio increases, and an increased reactivity to pressor agonists occurs. Sloughing of the endothelium occurs at a later stage in the disease process, where plaques become complicated, split or fissure.

Medial thickening in the aorta and the large arteries is associated with disruption and uncoiling of elastic fibres and an increase in the collagen, with calcium deposition resulting in stiff vessel walls. This decrease in the arterial compliance allows the pressure wave generated during systole to be transmitted through the arterial tree with an increased pulse pressure. The shape of the arterial waveform is also altered by early return of the reflective wave in late systole from the periphery, boosting the arterial pressure wave in late systole and so increasing the stress on the arterial wall. Reduced compliance of the large arteries also affects the carotid and aortic

baroreceptors that would normally buffer the rapid changes in BP. This complex process reflects the interaction of genetic and environmental factors previously mentioned, and attempting to unravel these experimentally is very complex. Whatever the mechanism the final pathway is common with an increase in peripheral resistance in vessels, secondary to a reduction in lumenal diameter associated with an increase in wall thickness.

There is also an association between the development of atheroma and BP, the higher the arterial pressure the greater degree of atheroma. This may be secondary to the local mechanical consequences of increased pressure and turbulence of blood flow, almost as a self-perpetuating mechanism. Abrupt increases in BP may accelerate atherosclerosis by causing premature plaque rupture in pre-disposed individuals.

2.5.1 Atheroma and The Cardiovascular System.

Angina and myocardial infarction usually occur secondary to atheroma. Left ventricular (LV) hypertrophy occurs as a result of the increase in size of cardiomyocytes, with increases in intercellular matrix that increases LV mass. These changes are associated with a poor prognosis, as a result of worsening ischaemia, more arrhythmias and reduced ventricular compliance, all predisposing to LV failure.

2.5.2 Atheroma and The Central Nervous System.

Cerebral atheroma may eventually lead to cerebral infarction. Haemorrhage occurs normally as the result of rupture of small intracerebral degenerative aneurysms, which develop in small perforating arteries in the region of the basal ganglia,

thalamus and internal capsule. There is hyaline degeneration in the aneurysmal wall and a defect in the media at its neck making it weak and prone to rupture.

Cerebral resistance vessels usually constrict in the face of increased pressure and dilate in the face of reduced pressure to maintain a constant flow (autoregulation). Resistance vessel hypertrophy seems to have a protective function in this respect so that the autoregulation range is increased in longstanding hypertension, and hypertensive encephalopathy may be seen and retinopathy is the commonest manifestation noted in the eye.

2.5.3 Atheroma and The Renal Tract.

Atheroma can affect the general blood supply to the kidney resulting in renal artery stenosis, or affect the microcirculation within the kidney itself. Renal microcirculation can be affected with arteriolar wall thickening and a resultant reduction in the diameter of the lumen. Hyaline degeneration is partially observed in afferent arterioles of the kidney, thickening the whole vessel wall, beginning in the subendothelial region and extending to the media. Progressive hyalinisation of the nephrons accounts for the progressive slow decline in glomerular filtration rate with age, which is accelerated by hypertension.

2.6 Biochemical Markers.

2.6.1 Atrial Natriuretic Peptide.

Atrial natriuretic peptide (ANP) is a hormone released from the atria in response to atrial distension, e.g. during large swings in pleural pressure. It is involved in cardiovascular and renal homeostasis, and has been shown to induce natriuresis, diuresis, to inhibit vascular smooth muscle contraction, and stimulate aldosterone and renin release.

In patients with OSAHS nocturnal polyuria is common [294], and when treated with CPAP this resolves. The mechanism for this is not clear, however ANP has been implicated. Conflicting data has been produced showing that ANP levels were high in OSAHS patients and resolve with CPAP treatment [295,296], and in other studies no difference in ANP levels before and after treatment were found [297].

2.6.2 Catecholamines.

Adrenaline (ADR) and noradrenaline (NA) are neurotransmitters excreted by the adrenal medulla, and NA is also excreted by sympathetic nerve endings, into the synaptic cleft. The nerve cell re-uptakes much of this NA but a proportion enters the systemic circulation and can be measured in the plasma, where levels reflect activity, however the circulating NA only reflects 5-10% of the total concentration. The measurement of plasma or urinary NA is used as an indirect marker for sympathetic

function but has been superseded by more sophisticated techniques of muscle nerve sympathetic activity (MNSA) and power spectral analysis of heart rate variability.

2.6.3 Nitric Oxide.

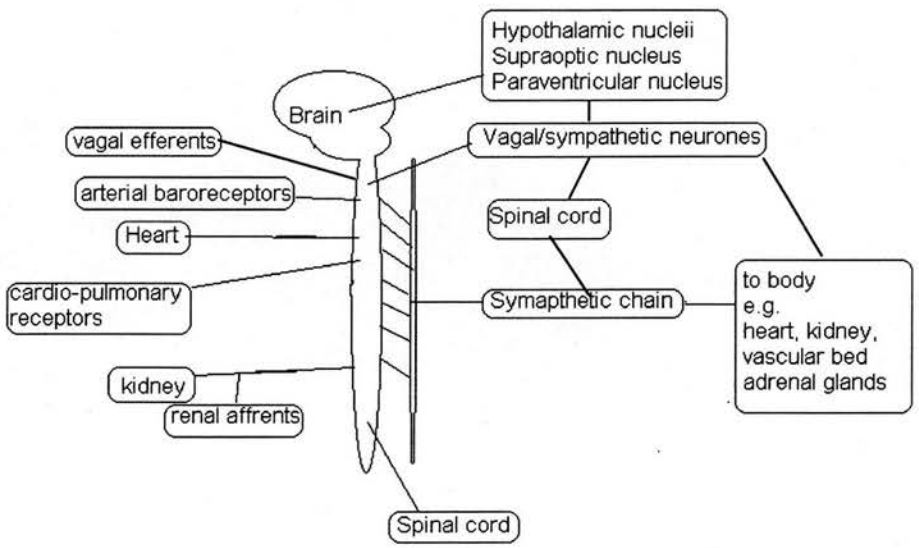
Nitric oxide (NO) is a very lipophilic gaseous molecule produced by a variety of tissues in the body and involved in the regulation of many different processes, including pain regulation, memory function, and as a transmitter within the genitourinary, gastrointestinal and respiratory tracts. NO also contributes to platelet aggregation, cardiac contractility and host defence with immunological functions. NO in the endothelium is partially responsible for the vasodilator tone that has an integral role in BP regulation. Theoretically there could be chronic alteration of vascular tone as a result of disordered nitric oxide production and signalling, leading to changes in vascular resistance.

2.7 The Autonomic Nervous System.

The autonomic nervous system (ANS) is a complex regulatory system within the body comprising two main parts, the sympathetic and the parasympathetic, these work antagonistically to control a variety of mechanisms.

2.7.1 Sympathetic Nervous System.

Figure 2.1 Diagram of Sympathetic Nervous System:



The Sympathetic Nervous System (SNS) has an integral role in the control of BP with varied actions. It comprises both an afferent and an efferent system sensing regulatory changes, and altering responses appropriately. Systemic arterial baroreceptors in large arteries form an efferent feedback loop via integrating centres in the medulla oblongata to influence areas in the hypothalamus and the reticular activating system, and are discussed further below. These nervous circulatory reflexes work to achieve sustained cardiac output and BP by complex mechanisms including mobilisation of blood from the vascular bed. In normotensive subjects the sympathetic stimulation of the heart and blood pressure is influenced by posture, activity, emotional state, fitness, and cardiovascular state. The peripheral vascular resistance is derived mainly from the arterioles, which are supplied by the SNS. Sustained increase in the vascular resistance may be mediated by a variety of

mechanisms led by the increase in sympathetic drive including; increased vascular resistance, increased cardiac output, sodium retention and renin release, vascular muscle defects either a membrane defect and or a problem with the synthesis of contractile protein.

Previous studies have suggested that the sympathetic nervous system has an integral role in the development of hypertension [298]. Early hypertension was characterised by increased cardiac sympathetic activity [299]. Genetically preconditioned autonomic over activity and stress probably play important roles in hypertension [270,300].

2.7.2 Baroreceptor Reflex.

Several reflexes within the cardiovascular system help control BP and heart rate, the main one being the baroreceptor reflex. Baroreceptors are stretch receptors located in the walls of major arteries including the aorta and carotid arteries. As the intra lumenal pressure increases these receptors are stretched and signal the brain to inhibit sympathetic discharge to the heart and blood vessels, altering cardiac output and peripheral resistance to allow the pressure to fall by means of negative feedback. The baroreceptors feed from the carotid sinus via Herring's nerve, the glossopharyngeal nerve, the tractus solarius to the medulla and those from the aortic baroreceptors feedback via the vagus nerve. In essential hypertension cardiovascular homeostasis is altered, but the causes are not fully understood, however early alteration in baroreceptor control suggests that the sympathetic system is integrally involved. Decreased sensory input from the carotid sinus and aortic depressor nerves cause labile or sustained hypertension. However it is not clear whether impaired

input from baroreceptors are a causative factor [301-305]. Arterial baroreceptors are reset in hypertension with a higher pressure threshold and reduced sensitivity to increases in pressure [274], as a result of the altered vessel wall dynamics.

Generally baroreceptors are not stimulated when MAP drops below 60 mmHg in the carotid sinus and 30 mmHg in the aortic arch [266]. Even a slight increase in BP can result in a large change in sympathetic outflow to correct the BP back to the 'normal' level. The baroreceptor feedback mechanisms function most effectively over the normal operating pressure range [266], therefore it is variable and can be reset. The role of baroreceptor resetting in the long-term regulation of BP is controversial, as it seems that it is reset within a short time. For example if the MAP was high there should be negative feedback to allow vasodilatation to encourage a drop in BP. However the baroreceptor impulses are marked when the BP is first increased but during the next few hours the level of activity decays and after 1-2 days it is back to a background level despite a high MAP, the converse is also true if the BP is low [266].

2.7.3 Chemoreceptor Reflex.

The chemoreceptor reflex is similar to the baroreceptor reflex however it is stimulated by changes in arterial pO_2, pCO_2 and pH. These receptors are located in the carotid and aortic bodies, and their nerves travel back along the same paths as the baroreceptor nerves. They signal back to the vasomotor centre and help regulate BP, and are especially important when the arterial pO_2 is low [306]. The carotid chemoreflex has two efferent outflows; via the phrenic motor output, and via the sympathetic outflow to both the heart and key vascular beds. The chemoreceptor responsiveness

can vary and has been shown to be altered in 32 patients with OSAHS [307] although these patients had co-existing obesity (mean BMI 34.2 Kg/m^2).

2.7.4 Muscle Nerve Sympathetic Activity.

Muscle nerve sympathetic activity (MNSA), is a measure of sympathetic nerve traffic to muscles used as a marker of sympathetic tone, and is usually measured in the peroneal nerve in humans. In healthy humans MNSA fluctuates about every 10 seconds, resulting in a rapid response in vascular smooth muscle and sino-atrial node activity, which in turn results in changes in heart rate and arterial pressure [308]. MNSA reflects approximately 50-69% of the variance in sympathetic activity it is also affected by breathing pattern and pleural pressures. Hornyak performed an experiment looking a the MNSA in normal subjects during the different stages of sleep [309] showing a reduction in activity during non-REM sleep and increased activity during REM sleep, which agreed with the previous animal studies [309]. Yamada studied MNSA in a hypertensive population and showed an increase in patients with hypertension at all ages and concluded that the SNS played an integral role in the maintenance of raised blood pressure [202]. In the absence of pulmonary stretch receptor induced inhibitory influence on sympathetic activity the MNSA response to hypoxia-induced chemoreceptor activation is greatly enhanced [310].

2.7.5 Heart Rate Variability.

Cyclical changes in heart rate and haemodynamic perameters has been recognised for more than 100 years. However it is only more recently that importance of

spontaneous fluctuations in heart rate has been recognised as a surrogate marker of autonomic function [311,312]. Heart rate has two main influences, intrinsic firing of the automatic pacemaker cells in the sino-atrial node, and the modulating influences of the ANS. The sino-atrial node is affected both by the SNS, which enhances the rate, and by the PNS, which suppresses heart rate. It is the balance between both these components, which results in the heart rate. This oscillation in the interval between consecutive heartbeats, the so-called heart rate variability (HRV), is used as a non-invasive marker reflecting sympathovagal balance. HRV can be analysed in a variety of ways, the two main ones being time domain analysis and frequency domain analysis (power spectrum) [311,312]. The R-R interval is mediated by fluctuations in sympathetic nerve activity, the higher R-R intervals rhythms are mediated by fluctuations in the vagal-cardiac nerve activity, and reflect events that provoke reciprocal changes of sympathetic and vagal neural outflows [311]. The R-R spectral power is calculated from a series of ECG recordings after a steady state is achieved using an autoregressive algorithm, taking 5-minute intervals. This produces centre frequencies and absolute power of component fluctuations.

2.7.6 Power Spectral Analysis.

Power spectral analysis uses the HR signal and converts it into its frequency components and quantifies them in terms of their relative intensity, called 'power' ($msec^2/Hz$), resulting in a power spectrum density of HR, which allows the separation of the components the autonomic nervous system. This is also affected by a variety of other factors including respiration, baroreceptor reflexes, vasomotor control and

thermoregulation. The analysis can be performed in two ways either by fast Fourier transformation (FFT) or autoregressive model estimation [312,313]. FFT gives discrete peaks for the several frequency components, the autoregressive method results in a continuous smooth spectrum of activity. Both methods yield similar results. The power spectrum consists of three major bands, which vary in definition between different authors [311-315]. However usually the high frequency (HF) band is 0.15 - 0.40 Hz, low frequency (LF) 0.04 - 0.15 Hz and very low frequency (VLF) 0 - 0.04 Hz. The HF band is associated with parasympathetic activity [311], the LF band is occasionally called the baroreceptor band because of its association with baroreceptor activity [311,312] and it has also been linked to thermoregulatory processes, peripheral vasomotor activity and the renin-angiotensin system. The VLF band had been identified as a marker for sympathetic activity [311], however it is poorly understood. Sympathovagal balance is taken as the ratio between LF and HF power. Therefore a reduction in the ratio suggests a shift towards vagal predominance and an increase in the ratio with a shift towards sympathetic predominance. A number of power calculations can be done. The total area under the power spectral curve represents total power of HR. The power of the individual components can be calculated by measuring the area under their peak on the curve. The absolute power can then be calculated from this. The HF component is the best understood [311], it must however be remembered that it is influenced by the degree of coupling between respiration and HR. The respiratory pattern could therefore influence the HF power, and in testing controlled breathing patterns can improve the reproducibility of the results.

2.8 Epidemiology.

Large studies have looked at the natural history of hypertension, most famously the Framingham series [316-318]. This large study found that borderline hypertensives – defined as SBP 140-159 mmHg and DBP < 90 mmHg - went on to develop hypertension and had a higher incidence of cardiovascular disease. The prevalence of this disorder in the United States is 20% of the population, with a new diagnosis rate of 3% per annum. The figures in the UK are similar. There are also large epidemiological cohorts showing that DBP is a good predictor for developing both cardiovascular and cerebrovascular disease, and not just within the 'hypertensive' confines but also in the normotensive population [112,113,319-324].

2.9 Morbidity and Mortality.

The most famous of epidemiological studies is the from the US, where the town of Framingham continues to be followed more than 50 years since the start of the project, with the investigators providing a wealth of data. In recent papers by one of the major investigators Kannel, he reports that BP elevation is a powerful contributor to all major cardiovascular sequelae [325-327]. The influence of SBP is well described showing a graded influence even at levels that are considered normotensive. Furthermore he reports that hypertension occurs in conjunction with other metabolically linked risk factors. Coronary disease is a major contributor to morbidity in hypertensives with 40% of events in men and 68% in women being associated with the presence of two or more risk factors. In isolation hypertensives;

14% of events in men and 5% in women occur in isolation without any concurrent risk factors [325,328]. This view has been confirmed by other studies [317,322,324].

Data from the Framingham study has suggested that SBP is a more important predictor of cardiovascular sequelae than DBP. Even mild to moderate elevations with normal DBP levels are associated with increases in morbidity and mortality [318,323,329,330]. Therefore by looking at DBP alone can be misleading and possibly lead to a false sense of security. It has also been reported from this cohort that persons with high-normal SBP (130-9 mmHg) and DBP (85-9 mmHg) have an increased risk of cardiovascular events, which is higher in men than women [322]. This reinforces that there is no lower threshold for improvements seen with reductions in BP [317]. This viewpoint has been challenged by Port et al, who reports an age and sex-dependent threshold for hypertension using a linear logistic regression model with the Framingham data [331], suggesting that a proportion of the population who would be thought to be at risk are not.

With an ageing population there is increasing interest in the older age group, the Framingham investigators analysed a cohort from their study looking at 6539 subjects who were free of cardiovascular disease and anti-hypertensive medication at baseline. They report a gradual shift from DBP to SBP and then to PP as predictors of cardiovascular risk. In the under 50 years DBP is the strongest predictor, then in the 60's all three indices are comparable, and from 70 years on DBP is negatively related to the risk so that PP becomes a better index than SBP [321]. Heart rate (HR), has been looked at to see if it is a useful predictor of cardiovascular mortality. A 5070 patient cohort from the Framingham group who were free from cardiovascular disease at study entry were analysed [332]. An association between a high resting HR

and cardiovascular morbidity and mortality was seen; this has also been reported in a number of prospective studies [332].

Night-time BP is an independent predictor of vascular disease in essential hypertension [271,272,333]. Perloff et al found that 24-hour BP was a better predictor of cardiovascular mortality and morbidity compared with isolated measurements, i.e. reduced white coat hypertension [334]. Systolic hypertension continues to be an important risk factor for death in the elderly where cardiac deaths were increased two to three fold. Systolic and diastolic pressures are independent risk factors and standard mortality ratios exist [335]. In more recent years there has been interest in the PP as an indicator for morbidity, with data suggesting the higher the PP the greater the associated cardiovascular risk [336-340].

Numerous studies have shown that with effective SBP control, the risk of cerebrovascular and cardiovascular events are reduced [201,317,319,341,342]. The evidence for DBP is also present but SBP is more closely linked with stroke, congestive cardiac disease, coronary artery disease, and renal disease [201,317,319,342,343].

Arterial stiffness increases with age, rising markedly after the 5th decade, resulting in a progressive rise in SBP and a fall in DBP as the vessel walls lose their elasticity [337]. The difference between SBP and DBP is the PP, and is a marker for large vessel stiffness. PP has been shown to correlate with the development of congestive heart failure in an elderly cohort [344], and is associated with an increased risk of myocardial infarction (MI), and cardiovascular mortality [337,338,340,345,346].

Mild disease is a common problem and even alone it is associated with a reduction in life expectancy. In severe disease the individual risk is increased and life expectancy is reduced further. The presence of malignant hypertension greatly worsens the

prognosis, as you would expect. The predominant cause of death is cerebrovascular and cardiovascular disease.

2.10 Symptoms.

Hypertension is usually asymptomatic. Headaches, although rare, are classically seen in the morning on wakening, occipital to frontal in position, and throbbing in nature. Epistaxis is uncommon although reported in the literature. Nocturia can occur as a result of a reduction in urine concentrating capacity within the kidney.

2.11 Clinical Examination.

The clinical examination in the hypertensive patient is often unremarkable, but should include auscultation of the heart and lungs, palpation of the abdomen and fundoscopy. BP should be measured and urinalysis performed. Weight and height should be recorded to allow calculation of BMI.

2.12 Diagnosis.

BP is usually measured non-invasively using a cuff placed around the upper arm, measuring the pressure indirectly in the brachial artery. The BP cuff size is important to ensure an accurate reading; the cuff bladder should be 80% of width and 40% circumference of upper arm [347,348]. The patient should be comfortable rested and relaxed, seated or supine, the arm horizontal at mid sternal level. A cuff that is too small will overestimate the pressure and one that is too big can underestimate the

pressure. Diagnosis should not be made on the basis of a single recording, at least two separate measurements on 2 separate occasions require to be done [347,348].

2.12.1 Investigations.

No simple blood test is diagnostic of hypertension, however blood tests may be important to exclude underlying pathology. Investigation should be used to exclude any underlying cause for hypertension that could be treated primarily, and should be targeted on clinical grounds, or to elucidate evidence of end organ damage. Thus renal function, urinalysis and ECG's are usually checked.

2.13 Treatment.

Non-pharmacological treatment of hypertension should ideally be instigated, with lifestyle measures including weight reduction, alcohol restriction, sodium restriction, exercise and behavioural therapy.

The pharmacological treatment of hypertension varies with the range of drugs available increasing rapidly. Finding the most appropriate drug for a patient may take time and ideally mono therapy is preferable, however often a combination is required. The British Hypertension Society has produced guidelines for the treatment of hypertension [349].

2.14 OSAHS and its Effect on Blood Pressure.

2.14.1 Pulmonary Arterial Hypertension and OSAHS.

The effect of OSAHS on the pulmonary vascular bed has been investigated in previous studies. In less than 20% of OSAHS cases daytime elevated pulmonary artery pressures develop and this may progress to right ventricular hypertrophy and rarely to cor pulmonale, especially in those subjects with pre-existing lung disease [350,351].

Early work from Hong using divers who were able to breath hold for up to 4 minutes, he reported the effects of this breath hold on alveolar gas exchange [352]. He showed a gradual decrease in PaO_2 while $PaCO_2$ increased during the first 30 seconds after which it levelled off. In OSAHS with each apnoea the gas-exchange is affected it would be reasonable to assume in a similar way to Hong's divers, with alterations in PaO_2, $PaCO_2$. Although it must be remembered that the divers were young and fit and therefore are a different population to the majority of OSAHS patients. Pulmonary vasoconstriction occurs in response to alveolar hypoxia in order to maintain lung perfusion with ventilation, resulting in repeated surges of pulmonary arterial hypertension overnight.

2.14.2 Systemic Blood Pressure and OSAHS.

2.14.2.1 Introduction.

The effect of OSAHS on systemic blood pressure has been the subject of many different studies, examining the effects on both night-time and daytime BP. The investigation of systemic daytime BP in OSAHS has provided considerable indirect evidence suggesting that OSAHS may lead to daytime hypertension, cardiovascular disease and cerebrovascular disease [65,79,82,353-358]. Despite the association suggested in the large epidemiological studies, OSAHS has not been proven to cause sustained daytime hypertension and whether it does is hotly debated [82,353,354,359].

2.14.2.2 Mechanisms of Acute Rise in Blood Pressure.

Acute rises in blood pressure around apnoea termination have been described by Davies et al [360], and these swings have a direct effect on mean night-time BP. The mechanisms involved in the genesis of the acute BP rise in OSAHS are complex with contributions from neuronal, hormonal, autocrine, paracrine events, along with effects of hypoxia and arousal [361].

The effect of arousal from sleep cannot be underestimated with marked changes in blood pressure which is the trigger for the repeated cascade of pathophysiological events that form the entity of OSAHS and the generate the sequelae of the disorder.

Apnoeas result in hypoxaemia and hypercapnia and thus stimulate the peripheral chemoreceptors, which in turn activate the sympathetic nervous system, increase cardiac output, increase systemic vascular resistance and blood pressure. As the

apnoea progresses SBP increases further, probably secondary to the hypoxia, and the heart rate drops (secondary to the diving reflex). Stimulation of the carotid body in the absence of stretch receptor activity reduces heart rate (Müeller manoeuvre), and at the moment of apnoea termination a further increase in SBP is seen. The maximum changes occur just after the apnoea termination, when the increase in systolic pressure could be more than 50%, increasing further with larger degrees of desaturation [362]. The BP rise takes 10-12 seconds to reverse after termination of the apnoea, via the carotid body and brain due to the circulation time [363]. SBP is usually lowest during the early and middle of the apnoea, with the pressure gradually increasing with a sudden rise at the apnoea termination [364]. With apnoeas of 40 seconds or more in duration the cardiac output falls by approximately a third [365]. This combination of increased SBP and reduction in cardiac output is associated with an increase in systemic vascular resistance [176].

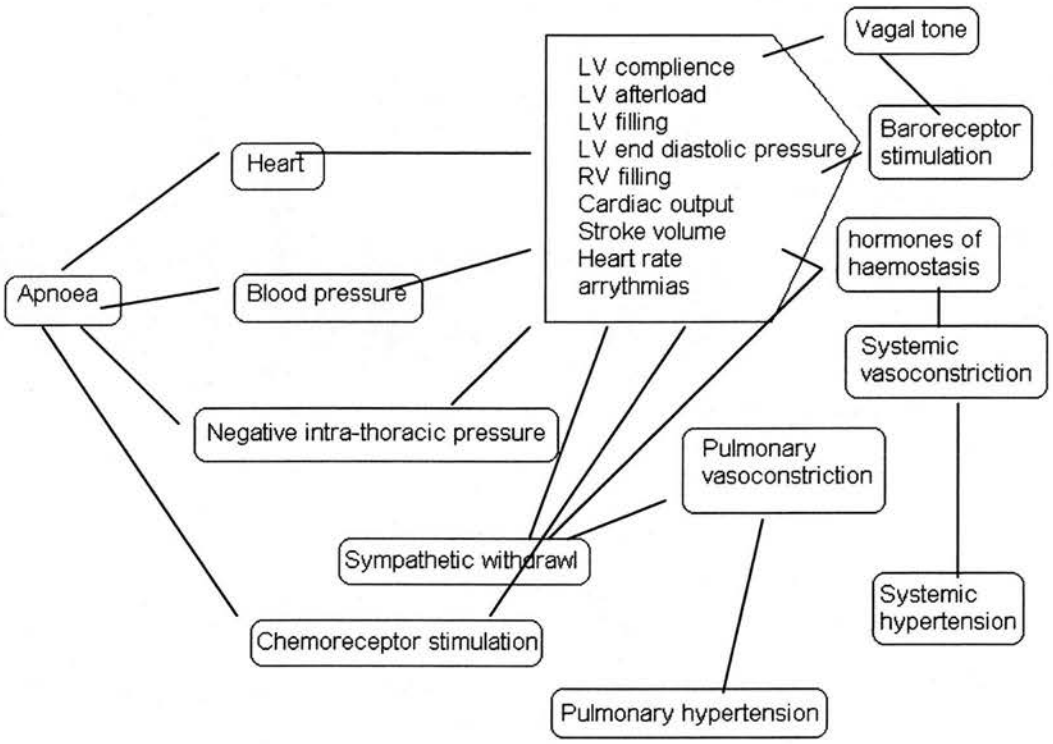
Systemic vasoconstriction is believed to be mediated by sympathetic neural activity [176]. The drop in pO_2 along with apnoea termination result in catecholamine release, which increases systemic BP and pulmonary BP, and the resulting sympathetic neural response leads to impaired cardiac sympathetic function and integrity. Termination of apnoea and the associated cortical and subcortical arousal leads to a rapid rise in the heart rate, which reflects the withdrawal of vagal tone due to baroreflex stimulation [366], systemic and pulmonary blood pressure rise [364], release of the hormones of homeostasis is triggered and arrhythmias can be initiated [367,368]. The generation of negative intrathoracic pressure during an apnoeic event results in sympathetic withdrawal and an initial reduction in systemic BP, because the sympatho-excitatory effects of the chemoreflex are unopposed, probably secondary

to a reduction in stroke volume, with associated cardiac deceleration [365]. The stress of the swinging nocturnal BP, associated with apnoeas and hypopnoeas is thought in particular to exacerbate pre-existing ischaemic heart disease and cerebrovascular disease [369].

The nocturnal changes can possibly produce a carry-over effect, which may persist into the daytime [370-372]. Therefore accurate timing of measurement is extremely important when performing investigations and it is important that the timings are consistent within a study. Increasing SNS activity, reducing baroreceptor sensitivity, accentuating vascular responsiveness, along with abnormalities in salt and water metabolism, all of these elements can contribute to hypertension, but whether they are affected by OSAHS per se remains unclear. The question of whether intermittent (sleep related) changes in BP (as seen in OSAHS) can lead to long-term elevation of daytime BP and structural cardiovascular changes also remains elusive.

The complex consequences of apnoea are illustrated in figure 2.3 overleaf.

Figure 2.3: Consequences of apnoea.



2.14.2.3 Possible Mechanisms of Sustained Daytime Hypertension in OSAHS.

The possible mechanisms of sustained daytime BP in OSAHS is the continued subject of debate and ongoing research, it involves many complex inter-related mechanisms. Earlier investigations have tried to control for BMI however they were small studies [207,373]. In performing this type of study it is important to take into account the variability of BP, and SDB, and the pattern of deposition of body fat.

Obesity associated hypertension is thought to be secondary to a combination of mechanisms inducing insulin resistance. Obesity and an increased caloric intake

increase the activation of the sympathetic nervous system secondary to hyperinsulinaemia. These increased insulin levels increase renal tubular sodium absorption and therefore sodium retention; it also results in vascular hypertrophy and attenuated vasodilatation in skeletal muscle.

One hypothesis for the evolution of hypertension is that SDB increases sympathetic nerve traffic. Clinical studies in SDB have shown patients with SDB have increased levels of sympathetic activity both in sleep and during wakefulness [163,374], this is discussed further in section 2.15. The acute increases in sympathetic traffic in apnoea and in the immediate post-apnoeic period have been demonstrated [375-377]. There also may be increases in sympathetic activity with arousal from sleep. It is important to dissect the mechanism of the sympathetic system involvement. Resting daytime sympathetic traffic is increased with OSAHS [378,379]. These studies although suggestive are small in size and not all have controlled for confounders [376,379] nor provided an adequate control population [374,377,378]. MNSA is a particularly difficult technique and the size and design of these studies in part reflects this. There has also been work looking at the biochemical markers of SNS activity which is further discussed in section 2.15.1.

These studies support a causal role of the SNS in the aetiology of hypertension in OSAHS patients. The aetiology of the increase in sympathetic drive is not clear but both hypoxia – acting via arterial chemorecpetors - and arousal from sleep have been implicated.

Chemoreceptors respond to episodic hypoxia and stimulate the sympathetic nervous system. The chemoreceptors may undergo adaptation to the long-term hypoxia and hypercapnia, thereby altering basal BP. Augmented ventilatory response has been

shown to hyperoxic conditions that can result in the inactivation of chemoreceptors [380]. A greater pressor response to hypoxia has been reported in OSAHS compared to non-OSAHS patients with hypertension [381].

Baroreceptor function seeks to maintain systemic BP at a given level. However this level may be reset. Whether the acute increase in BP seen with an apnoea can when repeated many times a night for years, reset baroreceptors leading to a higher daytime waking BP is unclear. From Brooks canine model there is some suggestion that the baroreceptor slope is not altered but is shifted to the right resetting at a higher pressure without a change in sensitivity [382], as is often seen in hypertension.

Other mechanisms for the development of hypertension in SDB include impairment of vascular endothelial function [383]. This has been studied using the model of forearm blood flow and vascular resistance to reflect vascular endothelial vasodilatation. Results suggested that endothelial dependant vascular vasodilatation is reduced in SDB subjects whilst awake [384].

There is emerging evidence that SDB may be associated with metabolic abnormalities, which are risk factors for hypertension, e.g. impaired glucose tolerance, insulin resistance, and altered cortiocotrophic function [385,386].

2.14.2.4 Does OSAHS Cause Daytime Hypertension?

Some investigators feel that the arousal from sleep is the critical factor in the possible development of hypertension in OSAHS patients [364,387]. However work by Brooks [388], using the dog model of OSAHS has suggested that hypoxia is a dominant force in the evolution of sustained daytime hypertension in this group of dogs at least. In their

study they did find an acute rise in systemic BP, both following apnoeic arousal and following sound induced arousals. However there was no sustained rise in daytime BP in the dogs exposed to acoustic arousal but there was when aroused by apnoea [388,389]. Hypoxia is sensed by the carotid chemoreceptors, which results in bradycardia, arteriolar constriction and catecholamine release, all of which cause transient hypertension [176]. Hypoxia is promoted as an important factor in the development of hypertension in the OSAHS patient, however patients with chronic hypoxia e.g. those who live at high altitude, or cyanotic congenital heart disease, do not seem to develop systemic hypertension [390], the reasons for this remain unclear.

2.14.2.5 Epidemiology.

Data from epidemiological studies demonstrates that hypertension is common in OSAHS patients [5,188,207,391-395] with incidences ranging between 48-96% of patients; and OSAHS is common in the hypertensive population with a quoted incidence of a 30-40% [188,207,393,396,397].

Larger epidemiological studies have been done; Carlson reported a cohort of 377 subjects, concluding that age, BMI and AHI are independent predictors of hypertension, and quoting relative risks (RR) of hypertension at 4.3 with age, obesity at 2.1 and OSAHS 2.1 [398]. Grunstein [54] in his cross-sectional study of 1469 subjects showed that AHI related to morning BP independently, and obesity and AHI were independent risk factors for hypertension. Hoffstein et al used multiple linear regression analysis to try and tease out the causes of hypertension in OSAHS, obesity

came out as the strongest predictor in his study. In the non-dipping OSAHS hypertensive patient, the mean 24-hour BP increased with RDI [9,399].

Hla et al [65,353,400] in a study of 147 normal working subjects, monitored 24-hour BP, defining hypertension as a SBP > 140, or DBP > 90 mmHg, controlling for age and weight. They reported a graduated rise in BP associated with an increase in apnoea frequency, and concluded that there was an association of hypertension in the OSAHS patients, even in the non-obese group, which was also independent of age and sex, reporting the relative risk of hypertension as between 1.5 and 2.5.

The Wisconsin sleep cohort continues to provide information in their prospective observational study. Young reported that seated BP increased linearly with AHI in their cohort of 1060 subjects [400], with an odds ratio (OR) for hypertension associated with an AHI of 15 events/hour slept as 1.8. Young et al [359] demonstrated a gradual rise both in ambulatory daytime and sleeping BP dependant on the AHI. This indicated that epidemiologically there is an increase in BP as OSAHS severity increases and conceptually that the severity of OSAHS is intrinsically linked to BP even in the normotensive patient. In Young's study [359] they showed that SBP and DBP increased with SBD severity in the unadjusted data. Using a multiple linear regression model to control for confounders their study continued to show that SDB severity measured as AHI was significantly related to both systolic and diastolic BP. They even demonstrated small changes in the mild cases with AHI's between 5-15, which is perhaps surprising. However as BMI increased the association was weaker [400]. Sorting out the dilemma of SDB and hypertension remains difficult because of the commonality of confounders. There have been 5 recent studies by Peppard [401],

Nieto [402], Lavie [190], Bixler [403] and Davies [404], concluding that there is an independent relationship between SDB and hypertension.

Peppard reported a follow-up from the Wisconsin sleep cohort [401]. The cohort has been followed up for 4 years in 709 patients and 8 years in 184 patients. They adjusted for baseline hypertension status, BMI, neck and waist measurement, age, sex, alcohol consumption and cigarette consumption. At follow-up the odds ratio for hypertension in comparison to an AHI of zero was: AHI < 4.9: OR 1.4; AHI 5 – 14.9: OR 2.03; and AHI > 15: OR 2.89.

The Sleep Heart Health Study is a large multi-centre prospective cohort study of SDB looking at risk factors for hypertension and cardiovascular disease [402]. Their cohort of 6132 subjects had seated BP and overnight PSG performed. Hypertension was defined in this study a BP of 140/90 mmHg and above, or the use of anti-hypertensive medication. BMI, neck measurement, waist-to-hip ratio, alcohol and smoking were all adjusted for. Between an AHI > 30 and an AHI < 1.5 there is an OR of 1.37 for hypertension. They also showed that the percentage sleep that the subject desaturated to < 90% pO_2 had an OR of 1.46 for hypertension. Although a very useful study it remains an observational one, with the BP recorded as an 'office' BP rather than a 24-hour recording. The authors did try to control for confounding as much as possible.

Lavie also reported a large prospective observational study of 2677 subjects who underwent PSG and BP recordings having been referred to a sleep centre [190]. Therefore these patients were not representative of the normal population as they must have been symptomatic to a degree to be referred to a sleep centre. Multiple regression analysis of BP was performed on subjects who were on no medication and

suggested that AHI predicted SBP, DBP after adjustment for age, BMI and sex. For every extra respiratory event, the OR of hypertension increased by 1%, and a 10% reduction in apnoea related desaturation increased the OR for hypertension by 13%.

Bixler [403] reported a population study, performing random telephone interviews on 16,583 subjects, selecting a subset of 1741 on the basis of having risk factors for SDB for a second phase. Sleep studies were performed on this cohort and they were stratified on the basis of their AHI; reporting SDB was independently associated with hypertension even when confounders were controlled for by logistic regression analysis. However the strength of this association decreased with increasing age and was in proportion to the severity of SDB. The BP recorded was supine 'office' BP taken after ten minutes of resting before the sleep study. Hypertension was defined in the study as SBP > 140, DBP > 90 or the taking of anti-hypertensive medication. The OR of moderate-severe (AHI ≥ 15) SDB having hypertension was 6.85, and with mild (AHI 0.1 - 14.9) SDB the OR was 2.29, comparing to their 'normal' control group. This study does not include a formal control group, the patients who had normal sleep studies were utilised, however by definition they had to be symptomatic or to have risk factors of the disorder, no attempt to match this population was made.

2.14.2.6 Studies in Hypertensive Populations.

Uncontrolled case reports of the resolution of daytime systemic hypertension in some treated OSAHS patients [405,406] support the causal role of apnoea in hypertension. Furthermore studies performed in the hypertension clinics have reported a higher incidence of SDB than seen in the population as a whole [407-410].

Olsen studied 441 subjects comparing BP in the hypertensives and hypertensives with OSAHS, and showed an OR of 3.8 with hypertension in patients with an AHI > 15 events/hour slept, however when adjusted for confounders this became insignificant [74], but the numbers of subjects with hypertension in this study were relativity small.

Kraiczi [411] performed a treatment trial of hypertension in SDB, in an alternative approach to the problem. Forty patients were enrolled in an incomplete balanced block design study. There were 5 agents from different classes of drugs studied, with each subject receiving two different medications for six weeks each, off CPAP therapy. BP was measured both in the clinic and with an ABPM, patients also underwent a sleep study. A significant reduction was seen in DBP with atenolol, the other drugs did not show any significant reduction in BP before and after introduction of the medication. Because the β-blocker was the only drug that reduced the DBP significantly the authors suggested that the sympathetic nervous system must therefore be involved in the pathogenesis of SDB [411]. Caution has to be observed with interpretation of these results as not all the data were supplied in the paper, despite recording 24-hour BP this was not included, and their primary

outcome was clinic DBP. Furthermore CPAP was not included as a possible treatment.

Worsnop et al studied a hypertensive clinic population to measure the prevalence of SDB in this population and compared them normotensive subjects [412]. They conclude that there is a relationship between OSAHS and hypertension, although in part they felt that this was explained by the confounders. The authors attempted to control for confounders, however the patient group contained both treated hypertensive and normotensive patients.

A cross-sectional study was reported by Grote et al [413], recruiting 599 subjects from a hypertension clinic and concluded that SDB should be considered in resistant hypertension especially in the younger patients (age ≤ 50 years). Clinic BP was recorded and patients had two home sleep studies performed. Once more this is observational data providing useful information but still lack the high level of evidence. The potential importance of considering OSAHS in refractory hypertension is also suggested in a study by Isaksson et al [414].

2.14.2.7 Studies in OSAHS Populations and Problems with Confounders.

There have been several studies which have suggested that the link is just co-incidental [82,354,415], and mainly due to confounders, however the studies were small in size and often lacked a control group. In general stronger relationships have been found in the under 50 age group [416]. There has also been several reviews looking at the association of OSAHS and diurnal BP [67,417-423], suggesting OSAHS may be a causal

factor for hypertension, however the problem of confounding variables exists, which can be difficult to control for. It is a difficult area to study as cuff BP react too slowly to show the lability of the nocturnal pressure in the situation of cyclical variation in OSAHS [424]. The nature of cuff BP can artificially elevate BP especially nocturnally using the ABPM however acclimatisation can occur, office BP can be elevated because of the 'white coat' effect. It is not clear which is the best predictor for the associated vascular sequelae, it is also not clear if the elevated BP associated with SDB has the same outcomes as elevated BP from other causes although it would be reasonable to assume that this is the case however no evidence to support this as yet. The increases noted in the nocturnal BP alone may be responsible for the possible increases in cardiovascular sequelae reported.

Increasing obesity is associated with increasing BP, especially if there is upper body fat deposition. The variation in night-to-night AHI makes the investigation of OSAHS more problematic as does the monitoring of BP in this group. This has been shown to weaken the relationship between BP and OSAHS by regressional dilution bias [425].

Pankow et al [426] recruited 93 subjects from their sleep clinic population, approaching alternative patients referred to the clinic. They performed 24-hour BP using an ABPM taking recordings at 15-minute intervals after the patients had attended for their sleep study. The sleep studies performed were limited relying on an oxygen desaturation index to diagnose SDB. They concluded that the desaturation index was significantly related to SBP and DBP both in the daytime and night-time. Utilising a multiple regression model they showed an independent association of oxygen desaturation and age to the daytime BP. The authors did not include any control

group in their study, comparing the different levels of oxygen desaturation index within his patient group. The patients were by definition symptomatic to some degree as they were attending a sleep clinic and therefore does not represent a normal population.

Grote et al [427] also recruited patients from a sleep clinic (n = 1190) to study the effect of SDB on BP. They recruited consecutive patients and recorded their office BP and performed home sleep studies. The authors report that RDI is independently and linearly associated with SBP, DBP and HR. The RR for hypertension increased with increasing SDB severity; OR of 4.15 for RDI $\geq$ 40 versus RDI < 5. The RR was increased in the younger population (age $\leq$ 50 years). They concluded that from their cross-sectional clinic data there is a relationship between SDB severity and SBP, DBP, and HR after controlling for confounders (BMI, age, alcohol consumption, cigarette smoking, cholesterol, daytime pO_2, and pCO_2). They did not include a formal control population in their study.

Mendelson retrospectively reviewed 619 consecutive admissions to a sleep centre [428], reporting that in the OSAHS patients the absolute minimum arterial oxygen desaturation was the most significant contributor to waking DBP, with weight also being additive. The authors did not control for confounders and did not attempt to include a control population. The author later reported further observational data in a further 265 patients [429]. Reporting that across the spectrum of SDB differences in DBP were associated with weight primarily, age and gender. In OSAHS DBP was associated with measures of SDB, namely AHI and minimum oxygen saturation. Once again no control population was included in the study, and confounders were not well controlled for.

Lavie et al recruited 38 consecutive patients from their sleep centre who had a diagnosis of OSAHS made from sleep study [430]. The authors monitored 24-BP 10 days after the diagnosis of OSAHS was made. They report that their results support a causal relationship between the severity of OSAHS and systemic hypertension, and that the severity of OSAHS is directly inked to the degree of hypertension. Once again no control population was included in the study, although the authors did try to control for confounders. The patient group was heterogeneous containing both normotensive and hypertensive patients on medication.

2.15 Sympathetic Nervous System in OSAHS.

Sympathetic discharge via the central and peripheral chemoreceptors during apnoea may be potentiated by the presence of hypoxia and hypercapnia, as the inhibitory influence of the thoracic afferent nerves are eliminated, and by arousal. Consequently the sympathetic vasopressor response increases with marked rises in BP with each apnoeic event [431]. This may be as a consequence of impaired baroreflex sensitivity, as baroreflexes exert an inhibitory influence on the chemoreflex response to hypoxia. Both hypoxia and hypercapnia exert local vascular effects resulting in vasodilatation, however these effects are opposed by the increase in the sympathetic neural traffic. This increased sympathetic activity seems to carry over into wake time, possibly leading to systemic hypertension. The vasoconstriction that occurs leads to an increase in venous return and therefore cardiac output (CO) is increased. This increased CO enters the vasoconstricted peripheral circulation raising arterial

pressure further. During apnoeic events the increased sympathetic activity in hypertensive patients is about 12 times the normal subject response [431].

There have been concerns previously that obesity alone may explain the increase in the MNSA suggesting that body fat was a major determinant of sympathetic neural discharge [432]. However in a study looking at 30 healthy obese subjects comparing them with 25 'normal weight' controls, no difference was demonstrated in MNSA in the different patients groups, OSAHS having been excluded using PSG [283], surmising that it must be related to apnoea. Fletcher reported that recurrent episodic hypoxia appeared to stimulate carotid chemoreceptors which in turn stimulates sympathetic nervous activity, which may remain stimulated after the event, giving a more prolonged effect [433].

Hedner et al [434], and Fletcher et al [435] both produced data to suggest that repetitive hypoxaemia plays a role in the aetiology of hypertension related to abnormal sympathetic tone, but it does not explain why the chronically hypoxaemic subject does not develop systemic hypertension. Hedner showed a potent pressor response to hypoxia in OSAHS patients that is not present in normotensive controls, which is in part related to the ventilatory response, suggesting a dependence on chemoreceptor function and sympathetic activation [381]. However this sympathetic response to hypoxia is demonstrated in healthy controls where BP remained unchanged, therefore perhaps the BP response in the OSAHS is more pronounced due to unopposed sympathetic activation or by another as yet unidentified mechanism. This suggests that sympathetic adrenergic activity is responsible at least in part for the increases in blood pressure [436]. Guilleminault et al suggested that SDB may be associated with

abnormal sympathetic discharge using muscle nerve sympathetic activity but also postulated that there may be impairment of local vascular endothelial mechanisms [437]. Narkiewicz studied the effects of chemoreflex activation on MNSA [438]. Controls were matched with OSAHS patients, concluding that tonic activation of the excitatory chemoreflex afferents may contribute to increased efferent sympathetic nerve activity to muscle circulation in this group of patients [439]. They also demonstrated increased sympathetic activity while awake, which increased further during sleep, and was reduced with CPAP treatment, however not back to normal levels. The controls were not matched for weight, only for age and sex. It is debatable whether the use of a split night study is adequate as patients had just commenced treatment, and sleep would not have been 'normal' [376]. It would possibly be better to allow the patients to have been established on CPAP for some time, or to restudy them at a later date to see if the MNSA had reduced further [376]. It is also interesting that work from the same centre reports a reduction in MSNA in OSAHS with CPAP use only after 6 and 12 months, which was not evident after 1 month of therapy [440]. This is contradictory to their previous study [376].

2.15.1 Biochemical Markers in OSAHS.

There has been many studies published in the literature looking at ADR, NA and ANP as markers of sympathetic nervous activity in OSAHS but these studies have their problems, as so many other things affect the levels of these hormones. Catecholamines levels in OSAHS have been demonstrated to be elevated and it was thought that these have a role in the genesis of the hypertension.

There is evidence in the OSAHS literature surrounding the measurement of ADR and NA levels both in the urine and plasma providing data with conflicting results. Fletcher et al showed that urinary catecholamines were reduced in patients with obstructive sleep apnoea and hypertension comparing pre and post tracheostomy values, and the absent diurnal variation of catecholamine excretion prior to tracheostomy returned post operatively [441]. Some investigators have found no reduction in urinary NA excretion [442], others have shown a marked decrease [443] in patients with OSAHS. Hedner reported raised NA levels in OSAHS patients during the daytime and Dinsdale et al also showed that 24-hour levels of urinary NA were significantly increased in apnoeics, but found no difference in plasma levels [444]. This study attempted to control for confounders, and included both normotensive and hypertensive patients with and without OSAHS. Ziegler [445] measured NA in 'normals' and in patients with OSAHS and hypertension in a study comparing NA levels when breathing room air, then a hypoxic gas mixture. This showed that the NA levels were increased in the apnoeics, with a greater response during hypoxia, concluding that the apnoeics were more susceptible to the transient increases in SNS activity, and the hypertensives maintained a higher baseline NA level.

ANP levels have also been measured showing that treatment with oxygen did not diminish the plasma level of ANP in SAHS [446]. This was a small study of only nine OSAHS patients and the authors did not report any evidence of increased ANP levels. This is contradicted by Krieger et al [447] who report a reduction in ANP levels in patients with OSAHS after the commencement of CPAP therapy. This was also a small study of 9 patients with severe OSAHS (mean AHI 94). No control group was included in either study.

2.15.1.1 Nitric Oxide in OSAHS.

Hedner performed studies looking at forearm plethysmography trying to work out the impact of NO on vascular tone in the OSAHS patient. The study reported an impairment of NO-dependant vasodilatation in the OSAHS patient independent of hypertension compared to matched controls, which is more marked in the hypertensive OSAHS patient [286,448]. Fletcher et al [435] looked at hypoxia in rats and demonstrated potentiation of the pressor response to hypoxia, concluding that NO mediated vasodilatation may be an important regulator of BP response to active hypoxaemia. Nitric oxide (NO) mediated vasodilatation was impaired in a study looking at OSAHS patients compared them to normals [286]. The changes in the sympathoadrenergic system and the vasodilatory action of the NO-dependant vascular relaxation may be of importance in the development of sustained hypertension in the OSAHS subject [449]. Schulz et al showed that plasma NO levels were reduced in OSAHS and were increased after commencement of CPAP both in the short and long term [450], this has also been reported by Ip et al [451].

Techniques have been developed to look at the exhaled breath NO, these have been utilised to study OSAHS patients, in a study by Olopade et al, they reported that exhaled nasal NO levels are increased after sleep in patients with moderate-severe OSAHS [452]. However conflicting results exist with a further study reporting no difference in exhaled NO in OSAHS patients compared to controls [453]. The control group had OSAHS excluded on 'clinical' grounds (no sleep study was performed) but were not otherwise matched, patients with OSAHS were older, heavier, and had higher SBP and DBP.

2.15.2 Baroreceptor Function in OSAHS.

A potential mechanism in the genesis of hypertension in OSAHS patient is the adaptation of the baroreceptor function in response to repeated swings of BP with apnoeic events and variation of pO_2. In disease there may be resetting of the baroreceptors peripherally or centrally which may be slow to return to normal levels, and perhaps do not fully normalise with treatment of the underlying disorder.

Parati et al [454] concluded that spontaneous baroreceptor reflex sensitivity was depressed in severe OSAHS, suggesting that in such patients baroreflex dysfunction and chemoreceptor stimulation by hypoxia may be involved in the increase of sympathetic nerve activity occurring during sleep. Carlson showed a reduction in baroreceptor sensitivity, both in normo and hypertensive OSAHS subjects, and showed an impaired response to hypotensive stimuli. Results suggested that this represented an adaptive response to the changes in blood pressure or hypoxia associated with the nocturnal apnoeas, which may contribute to the increased MNSA [305]. A further study of matched OSAHS patients with controls looking at the baroreflex control of MNSA and HR was performed. The authors concluded that the patients with OSAHS have impaired baroreflex sympathetic modulation, but the control of HR was not impaired [455].

In the canine model of OSAHS, Brooks demonstrated the resetting of baroreceptors to a higher pressure but did not show any change in the baroreflex sensitivity [382].

2.15.3 Muscle Nerve Sympathetic Activity in OSAHS.

Microneurographic studies in both OSAHS and hypertension have provided data suggesting a 24-hour dysfunction may exist in the control of the autonomic nervous system with an abnormal number of sympathetic discharges at a high level not only during sleep but also in wakefulness [310,378,456,457]. This abnormal and continuous stimulation by sympathetic nerves may increase peripheral vascular resistance and can be associated with the development of hypertension. An increase in nerve traffic has been demonstrated during apnoeas, peaking early in the recovery period and thereafter shutting off abruptly [376]. This occurs probably as a result of the interaction between the peripheral chemoreceptor stimulation and cortical arousal.

Carlson et al also examined MNSA recorded in wakefulness in a small group of 11 patients with OSAHS, half of whom were also hypertensive and on anti-hypertensive medication which was stopped, followed by a washout period of at least 3 weeks prior to study commencement. MNSA recordings were increased in these patients compared to matched controls, and no difference was found between the normotensive versus the hypertensive OSAHS groups. SBP but not DBP correlated with MNSA. The authors did not investigate the effect of at a treatment on MSNA [378].

Hedner [458] examined sympathetic activity, cardiac structure and blood pressure in severe OSAHS patients on CPAP. This study demonstrated in a small group of patients with well-matched controls, elevations in sympathetic neural activity with each apnoeic event, with a decline in activity at the termination of the event. Furthermore they showed that treatment of OSAHS with CPAP led to a reduction in

MSNA, suggesting that sympathetic control of vascular tone may be modified in OSAHS. This study also postulated that the response might involve the release of circulating catecholamines as well as a neural sympathetic response mediated via a carotid body reflex. They monitored CPAP use by self-reporting, and measured plasma NA, both in the day and at night, along with MNSA and cardiac structure. The authors concluded that a decrease of sympathetic activity was not associated with blood pressure change or cardiac structural change, thus contradicting previous reports [459]. However it was a small study (n = 6) with subjective CPAP use, and the tests were performed during the daytime, which may have confounded results.

Waeavdekar et al [460] examined muscle nerve sympathetic activity in OSAHS. Activity was measured in wakefulness before and after at least one month of compliant CPAP therapy. Although this uncontrolled study had a small sample size (n = 7), a reduction in MNSA was reported. This reduction was most marked in patients who used their CPAP for ≥ 4.8 hours a night, and there was no change in the non-compliant patients [457].

The role of the SNS in the aetiology of hypertension in OSAHS remains unclear. The current data provides conflicting results, which are partially due to the study designs and a reflection on the difficulties in performing the investigations, and recruiting patients into the trials.

2.16 Endothelin in OSAHS.

There is no increase demonstrated in ET-1 levels in OSAHS in a study by Grimpen and colleagues [292]. This study looked at 29 patients with matched controls measuring

the ET-1 levels before and after treatment with CPAP. It was a mixed group of patients including treated hypertensives and patients with cardiac disease, though they attempted to match for this in the control group. They did not show any difference in the ET-1 levels. However much of the ET-1 is produced ablumenally and therefore may not be recorded in a plasma sample, and the short half life of the hormone makes the measurement difficult, requiring prompt handling of the blood samples.

A smaller study was reported by Saarelainen et al [293], including a mixed group of OSAHS patients both with and without hypertension, comparing ET-1 levels with an unmatched population of normal controls. They showed that patients with OSAHS have higher levels of ET-1, but this did not decrease with CPAP therapy. More recent work by Phillips [291] also showed increased levels of ET-1 in patients with OSAHS, however they also demonstrated a reduction of ET-1 with CPAP therapy. This was contradictory to Grimpen's data. Their protocol differed from the previous studies as they employed a split night sleep study/CPAP titration study, so sleep stage effects could confound the result. The patient group in both studies also included treated hypertensives, even allowing for medication withdrawal and washout, some irreversible changes may have been present which all adds to further confound the results. It is clear from these conflicting results that further work needs to be done in this area.

2.17 Animal Models.

Using an animal model can be useful in studying OSAHS, allowing more sophisticated experiments to be undertaken that would not be possible on human subjects. The first animal model of OSAHS was developed in the rat by Fletcher [461], who induced severe hypoxia without airflow obstruction and demonstrated a sustained systemic BP rise. However this was only seen in certain strains of rats, suggesting there is a probable genetic influence. The rats were exposed to short repetitive bursts of hypoxia and demonstrated considerable sympathetic activation, and they concluded that the hypoxia alone may be responsible, however they were not able to demonstrate the elevated NA levels seen in other studies [461]. BP changes were blunted by chemical sympathectomy, and with carotid denervation no BP increase was noted [462]. These studies suggested that chemoreceptor function plays an important role in the genesis of the hypertensive response [435,463]. Although a very useful model for OSAHS, the animals exposed to repeated hypoxia did not suffer all the physiological events of the frustrated respiratory events.

The best animal model to date is the canine model developed by Brooks [388], which comprises a complicated set up of telemetered EEG, and a tracheostomy that occludes automatically when the dogs EEG indicates sleep, opening up once again when the dog arouses from sleep. This is all performed remotely so that the dogs are 'free living'. The studies simulated an AHI of approximately 60 events per hour, for 8 out of 24 hours. This study demonstrated for the first time a direct link between sustained daytime hypertension and apnoeas, and also demonstrates that recurrent acoustic arousal from sleep did not cause daytime hypertension in dogs at least [388],

although acoustic arousal did result in transient "nocturnal" blood pressure rises. Brooks demonstrated a mean increase in diurnal BP of 15 mmHg over 100 days. The group also demonstrated that these levels fall back to pre study levels after the study was completed and apnoeic insults were removed, occurring at different rates in the different dogs. It was a small study with only 4 animals so far.

O'Donnell et al [464] also produced a canine model of OSAHS reporting an increase in MAP over time with airway occlusion in a sleeping dog, which could be accentuated by prior sleep deprivation, and that this raised MAP is sustained for at least 2 hours after airway patency is normalised. Their model was similar to the Brooks one, however the dogs were a little more restricted as telemetry was not employed and the dogs were therefore chronically instrumented and wired up to the equipment.

Brooks study [388] was the first to show in a prospective manner evidence of OSAHS being a causal factor for daytime hypertension. Mechanisms responsible for the conversion of acute pressor responses to nocturnal apnoea into daytime systolic hypertension remain elusive but theories exist to a causal role; with arousal, hypoxic chemoreceptor stimulation, and the large swings in intra-thoracic pressure all featuring.

In the Brooks study acoustic arousals alone did not show the daytime increases in BP seen in the OSAHS model with the apnoeic arousal [388]. This, combined with Fletcher's data in the rat model [435,462,463], suggests that for nocturnal respiratory events to result in daytime hypertension, hypoxaemia is a necessary component.

2.18 OSAHS Treatment and its Effect on Blood Pressure.

Many studies [356,357,405,434,442,465,466] have all attempted to try and unravel the association between OSAHS and hypertension. Only one study by Engleman included a proper control population [242].

Early studies looking at BP changes are based on tracheostomised patients, and later studies were performed looking at the effect of CPAP on BP in this patient group. Several "before and after" studies published in the late 1970's reported OSAHS patients treated with tracheotomy then in the 1980's with CPAP, demonstrated an improvement in hypertension, and/or a reduction in the medication requirements [357,465,467,468]. A reduction in BP after tracheostomy was shown in adults by Lugaresi et al [469], who reported two non-obese patients showing that their breathing pattern normalised post treatment and their pulmonary arterial pressure normalised. Guilleminault also wrote a review in the mid 1970's stating that it had been shown that OSAHS caused hypertension, by reductions in BP in tracheostomised patients [383,467]. Motta et al [467] reported the receding of hypertension after tracheotomy in adult OSAHS patients. He studied 6 patients with OSAHS before and after tracheostomy, and showed that the haemodynamic effects and hypoxia noted in the patients pre procedure improved with the tracheostomy. The patients were studied on single nights, and it was not clear if there was a lag before the subject was restudied post tracheostomy. Although these studies are suggestive of a link between OSAHS and hypertension they were uncontrolled case reports and thus do not provide an adequate level of evidence.

CPAP abolishes the nocturnal BP swings and reduces mean nocturnal pressure [406,470]. However the effect of CPAP on the daytime or overall 24-hour pressures has remained unclear with conflicting evidence being published. Tilikan reports a reduction of both SBP and DBP during the daytime following CPAP treatment as did [395], Motta [467], Suzuki [465], and Wilcox [357] but again these studies were neither randomised nor controlled.

Akashiba reported 5 case studies, measuring BP every 20 minutes for 10 days after commencement of CPAP therapy. Only severe OSAHS patients were studied, and for analysis the patients were separated on the grounds of their BP into dippers and non-dippers. The conclusion was that CPAP caused a nocturnal drop in BP in both groups. The study was small and patients were not randomised to take part and no control group was included [468]. Akashiba reported a further study with 30 OSAHS patients, a third of which were hypertensive- who had their medication stopped 3 days prior to study entry [466]. The hypertensive group had a higher BP at baseline, they were treated with 2 weeks of CPAP therapy, then had a single BP recorded between 10-11a.m. using the same observer. CPAP use was not reported and there was no control group or placebo arm included. The study concludes that daytime hypertension was partially induced by OSAHS and it was reversible with CPAP therapy. Although a bigger study it still contained flaws with the short treatment time, lack of control or randomisation. In addition major bias must be introduced with the single readings of BP.

After effective treatment of OSAHS with CPAP, Guilleminault et al reported that BP was reduced but not back to 'normal' levels [248]. Jennum [405] found that morning and night BP decreased in 14 OSAHS subjects treated for 7 days with CPAP. The study

group was selected from the sleep centre cohort, and had to be on no medication, BP recordings were taken invasively with an intra-arterial line, no randomisation was performed neither was any form of control included into the study. Mayer [406] treated 12 men with OSAHS for 6 months and observed a significant drop in systemic pressure with treatment. A further study by Hedner et al [434] looked at a similar group over 20 months and showed no decline in 24 hour blood pressure or left ventricular mass, despite showing a significant drop in adrenergic activity. However no objective CPAP use was recorded.

A study by Wilcox [357], showed that BP was reduced at 8 weeks in patients who used their CPAP, both in hypertensive and normotensive groups. This was a small study (n = 9), which included both normotensive and hypertensive patients with OSAHS. BP was recorded using an automated ambulatory device, and patients acted as their own controls. The authors excluded non-CPAP compliant patients. Reporting a drop in SBP in the daytime as well as night, and DBP in the daytime only, not surprisingly patients who did not comply with therapy demonstrated no drop in BP. They concluded that OSAHS was an independent factor in the development of hypertension.

A further study by Mayer [406], reported a reduction in SBP, DBP and reduction in variability of BP, in both sleep and wake times, he concluded that hypertension in OSAHS was reversible at least partially. This was also a small study (n = 12), which included hypertensive patients who had their medication stopped prior to study commencement. BP was measured at baseline and after 6 months of CPAP therapy. Patients were therefore off their hypertensive medication for at least 6 months. It is

debatable that they would not perhaps need the drugs if their OSAHS were treated however this is as yet unproven.

Suzuki reported data from 9 patients with OSAHS [465], recording their BP before and during CPAP therapy for 48 hours using an ambulatory device. This small group was heterogeneous including both hypertensive and non-hypertensive patients. He concluded the decrease recorded in the BP was seen only in the hypertensive group not the normotensive population, as was the reduction in HR. The authors concluded that CPAP improved BP in some hypertensive OSAHS patients. The study included no control population and it was not randomised [465].

A study of 60 hypertensive patients with OSAHS concludes that reductions in BP in this group are more closely linked to weight reduction than CPAP use [356]. It was not a well-designed study; many of the patients were asymptomatic as they were identified from the hypertensive clinic population. The patients self selected which group they would go in with half the patients declining CPAP therapy, and were then just given advice on weight loss. BP recording were taken from GP records for baseline, and recorded last thing at night and first thing in the morning manually, which introduced observer error. The authors failed to comment on how many different people were involved in collecting the data and whether inter-observer error was an issue.

Ali studied a small cohort of patients (n = 8), using a portable beat-by-beat BP device, and compared BP during wake, OSAHS, OSAHS with supplemental oxygen, and with CPAP therapy. He concluded that CPAP did not reduce MAP but reduced the oscillations. The study was not randomised, and the recordings were only taken

for a period of 30 minutes each, which may not reflect the true severity of the disorder, as this data collection method does not take account of sleep stage [470].

Dimsdale et al [471] reported data from 39 patients, from their parallel study employing 'sham CPAP'. Patients had ambulatory BP monitoring at baseline and after a week of CPAP therapy. Results demonstrated a reduction in daytime MAP in both groups and a reduction in night MAP with CPAP therapy. It is a little surprising to discover that CPAP is as good as 'sham CPAP', suggesting that the placebo effect is strong.

Stradling et al approached the problem from a different direction, trying to see if OSAHS is a causal factor for hypertension [372]. They selected 6 patients from their clinic with OSAHS, already established on CPAP therapy, and altered the CPAP pressure between therapeutic and sub therapeutic (down to 3 cmH_2O) over 5 consecutive nights, keeping the proportion of therapeutic CPAP constant for each night. BP was recorded after the 5th night, using an automatic device by the same observer. They concluded that acute changes in awake BP can be caused by OSAHS, and that the effect may wear off as the day goes on. It is an interesting approach to the problem, but once again the study was small. In providing sham CPAP this may in effect treat some of the events, and the patients for part of each night received correct pressure CPAP therapy. Both these factors may have masked the effect on BP.

There is a school of thought that the increase in the nocturnal BP is carried over into the morning and resolves by late afternoon or evening. However later studies by Guilleminault and Suzuki [8] do not show a significant decline in blood pressure with CPAP after 4 months therapy.

Hedner [459] studied 12 patients over a 20-month period on CPAP therapy and did not demonstrate any reduction in 24-hour BP or LV mass, but showed a significant reduction in sympathetic activity. CPAP therapy was not objectively recorded. Wilcox [357] studied 19 subjects and showed a reduction in BP after 8 weeks of CPAP in a compliant group. Jennum [405] looked at a very small group (n = 14) and showed a reduction in BP, this however disappeared when the data was controlled for weight. The only prospective controlled trial was from our own centre [242], which was small (n = 13), and compared CPAP with an oral placebo measuring 24- hour BP at the end of each treatment limb. No decrease in BP was noted, however a small but significant drop in daytime MAP was found.

Davies carefully matched 19 severe OSAHS patients and 19 snorers without OSAHS with normal controls [472], and showed no difference in 24-hour BP between the groups, although did show a significant increase in night-time SBP in the untreated OSAHS patients. LV mass between the groups was not significantly different. OSAHS patients were restudied with 24-hour ABPM after commencement of CPAP therapy, and showed a significant fall in nocturnal SBP. Echocardiographic measurement of LV mass is difficult and is calculated from a formula after dimensions are measured echocardiographically. There are several areas open to observer error with this method of LV mass estimation. The authors did attempt to allow for this and performed reproducibility studies.

Davies et al performed a study of 45 patients with OSAHS carefully matched controls without OSAHS, matching for BMI, age, alcohol consumption, cigarette smoking and IHD. 24-hour ABPM was performed and showed a significant increase in daytime and night-time DBP and night-time SBP in OSAHS patients. There was a

slight difference in body fat distribution between groups, with the control group having more upper body obesity [404].

In contrast to these uncontrolled and non-randomised studies Engleman et al [242] looked at a small group of 13 patients who received three weeks of CPAP (mean use 4.3 hours) in a randomised placebo controlled crossover design. 24-hour BP was recorded using ambulatory devices. No significant decline in BP was observed over the 24-hour period but the power of this study is relatively low, and it included a very heterogeneous group of patients.

Stradling et al concluded in a review that OSAHS will be shown to be a small independent risk factor for daytime hypertension [424], and perhaps its associated complications.

The BP's did not all return to normal with treatment and this fact has been used in the argument that there was no interaction between SDB and increased BP [67]. It is possible that the trigger factor for BP increase is the SDB, perhaps triggering a cascade of events, some of which may be irreversible, or that the length of time suffering for SDB without treatment leads to irreversible (hypertensive) damage as a result of which BP levels cannot fully come back to 'normal' levels. However the recent large epidemiological studies have helped reinforce the role of SBD as a probable independent risk factor for hypertension [353]. It is possible that these poor results reflect the irreversible vascular damage that preceded treatment of OSAHS, or that studies did not take in to account the potential of the confounding factors.

The diversity of the different studies and their conflicting results is a reflection of the difficulty in providing a good level of evidence with well-constructed properly powered trials in this area. When the studies reported in this thesis were designed

there were no adequately powered, randomised-controlled studies of the effect of treatment for OSAHS on 24-hour blood pressure.

2.19 CPAP and The Sympathetic Nervous System.

Current evidence suggests that OSAHS causes increases in sympathetic traffic; so treating patients with OSAHS should result in a decrease in SNS traffic. Several studies have examined the effect of CPAP on the sympathetic nervous system in OSAHS.

Jennum reported a reduction of plasma NA and normalisation of BP after 7 days of CPAP in an uncontrolled study [405]. Hedner studied twelve severe OSAHS patients in an open long term follow up study. 24-hour BP was monitored along with NA levels in the plasma and urine. The study concluded that in untreated OSAHS the sleeping and wake levels of SNS activity were elevated although falling with CPAP treatment the levels did not return to normal [456]. The study was small with only 14 subjects, was not randomised nor controlled and analysis was not performed on an intention to treat basis with one patient being excluded because of poor CPAP use. A mixed group of patients were enrolled including a hypertensive population, withdrawing anti-hypertensive medication for 3 weeks prior to study. A reduction in the biochemical markers of sympathetic function was noted. The study failed to show a change in either BP or LV mass index (computed from echocardiographic measurements). However BP was studied after only one night of CPAP and this may have been too early find the maximal response. This work was echoed by Somers [376], who produced a study comparing MSNA in patients in wakefulness and sleep before

and after CPAP therapy [376]. He also showed the high resting wake sympathetic neural levels, which increased further with the onset of sleep and demonstrated a reduction in sympathetic neural activity with one night of CPAP treatment.

Waravdekar et al studied at a small group of 7 patients with OSAHS measuring MSNA in wakefulness before and after one month of CPAP. He showed a reduction in MSNA in patients who complied with therapy [460]. Narkiewicz went on to study the MSNA in patients before and after 1, 6 and 12 months of treatment with CPAP, comparing them to an untreated group of OSAHS patients. They did not have a control group of 'normals', nor did they match their untreated group with the CPAP group. They reported no changes in either heart rate or BP over the study period in either group [440]. They demonstrated a drop in sympathetic traffic in the CPAP group at 6 and 12 months compared to the untreated group, concluding that CPAP decreases MSNA in OSAHS patients with prolonged therapy. The numbers studied are small with only 11 patients in the CPAP group and 9 in the untreated group. Interestingly this conflicted with data produced by the same centre which showed a drop in sympathetic traffic with CPAP during a split night sleep study [376]. The small numbers partly reflect the difficulty in recruiting patients to this invasive study and the technical problems carrying it out. This study also raises ethical concerns about not treating OSAHS patients for a year while the study is underway, however they used the patients who declined CPAP treatment, therefore producing selection bias, and did not offer any other form of therapy. The BP recordings were taken over a 10-minute period at 1-minute intervals using an automatic sphygmomanometer. There was no comment about the time of day and whether this was constant between the different recordings and different patients. The CPAP use was self reported and

therefore not objective, and this may in part explain the lack of changes in HRV and BP, as the patients generally tend to overestimate CPAP use [473] and may have been poorly compliant.

2.20 Discussion.

The regulation of BP is a complex process, which involves many different systems. OSAHS invokes a range of physiological actions that also affect BP. Patients with untreated OSAHS have hundreds or even thousands of blood pressure swings per night. However with the number of confounding factors it is very difficult to prove whether OSAHS itself is a determinant of BP, and also whether it has effects that continue on into the waking hours. It is also apparent that there have been no adequately powered randomised controlled trials on the effect of CPAP on BP in OSAHS.

How could nocturnal alteration in blood pressure lead to daytime hypertension? Target organ damage in hypertensive disease is related not only to the MAP but also to its variability, and the loss of dipping [271,474]. Could the resulting vascular damage lead to sustained daytime hypertension? Alternatively, is baroreceptor function reset as a result of the intermittent nocturnal hypertension?

The major question this thesis set out to answer was to see if OSAHS is a determinant of daytime increases in BP. If it is proven that OSAHS is a cause of sustained hypertension this will have significant Public Health implications.

With the exception of Davies study [404], the recent studies are observational in design, although giving good epidemiological data on an association between OSAHS and

hypertension, good evidenced based studies still need to be done. The mechanisms of BP control and the abnormalities in OSAHS remain elusive [284]. Further investigation into:

- The effect of episodic hypoxia and hypercapnia on chemoreceptors and the sympathetic nervous system;
- Resetting of baroreceptor function;
- Modification within the cardiovascular system;
- The effects of stress from arousal and sleep disruption;
- Endothelial cell changes and vascular remodelling

are all required to improve the knowledge base and aid our understanding of the disorder. The development of hypertension in the OSAHS patients is a slow process and because of this it is difficult to study.

Chapter 3.

Daytime Function.

3.1 Introduction.

The effect of sleepiness on daytime function has been reported, and the impact on day-to-day living has been increasingly recognised. Marked sleepiness can be associated with accidents in the home, the workplace and on the road. Large epidemiological studies have investigated the impact of SDB on neuropsychological function [137], concluding that the degree of SDB correlated significantly with the deficiency in psychomotor function. Cognitive impairment has also been shown in this patient group [4,135,141,143,144,475,476], with significant improvements when treated with CPAP [133,135,136,144,239,477].

3.2 Measures of Daytime Sleepiness.

3.2.1 Epworth Sleepiness Scale.

The Epworth sleepiness scale (ESS) [478] was developed as a tool to measure subjective sleepiness, in an attempt to distinguish between tiredness and sleepiness in a variety of day-to-day situations. This was also introduced to provide a universal tool to allow easy comparison between different treatments and between different research projects. It does not however differentiate between different causes of sleepiness. It has been validated [129,130,132,479,480].

It is a subjective self reported questionnaire, in which the subject are asked to score themselves on a scale of 0-3 in eight different situations, 0 corresponding to never falling asleep in that situation, to a maximum of 3 corresponding with always falling asleep in the situation. The maximal score being 24, the higher the score the sleepier the individual. The scale is included in figure 3.1 overleaf.

Figure 3.1: The Epworth Sleepiness Scale.

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how that would have affected you. Use the following scale to choose the **most appropriate number** for each situation.

Scale

0 = would ***never*** doze
1 = ***slight*** chance of dozing
2 = ***moderate*** chance of dozing
3 = ***high*** chance of dozing

Situation	**Chance of dozing**
Sitting and reading.	_____
Watching TV.	_____
Sitting inactive in a public place. (e.g. a theatre or a meeting).	_____
As a passenger in a car for an hour without a break.	_____
Lying down to rest in the afternoon when circumstances permit.	_____
Sitting talking to someone.	_____
Sitting quietly after lunch without alcohol.	_____
In a car, when stopped for a few minutes in the traffic.	_____
Total	_____

Thank you for your co-operation

3.3 Quality of Life.

Quality to life (QoL) is an important factor in general wellbeing, both physically and emotionally. Many different tools exist to measure quality of life, in this study a sleep specific questionnaire is employed. Previous studies have tried to quantify the impact of OSAHS on QoL [146,156-159]. These studies have all concluded that OSAHS has a significant impact on quality of life, some comparing OSAHS with other common illnesses, such as asthma and showed that the different domains improve with treatment [481].

3.3.1 Functional Outcomes of Sleep Questionnaire.

The functional outcomes of sleep questionnaire (FOSQ) [482] is a sleep specific questionnaire developed by Weaver et al, designed to try and quantify the impact of EDS on day to day life. It comprises a self-administered questionnaire that contains 30 questions (encompassing 74 items), taking approximately 15 minutes to complete. For this study the optional questions on sexual health were omitted as it was felt that my patients may be uncomfortable with them. A copy of the questionnaire is included in appendix 1.

The definition of functional status chosen by the authors was "everyday behaviours encompassing the areas of physical, mental, and social functioning in daily life". The words sleepy and tired are defined in the instructions read by the patients before completing the questionnaire. Subjects are then asked to mark the most appropriate score pertaining to themselves at the time of the study in reply to each question stem, ranging from "no difficulty" to "extreme difficulty". The questionnaire is then

scored using a mean-weighted system, within each subscale using only those activities that are participated in, allowing for skipped questions. These scores are amalgamated to produce a global score. The lower the score the more sleepiness is impacting on the QoL in that individual.

The five different domains are:

- activity level (9 questions),
- vigilance (7 questions),
- intimacy and sexual relationship (4 questions),
- general productivity (8 questions),
- social outcome (2 questions).

With the mean weighting system each of these domains provides a score out of 4, resulting in a global score of 20 (16 in our case). The normative data for this test is taken from a group of normal subjects who did not have OSAHS. Global scores in this group of normals are all above 17.5 (ex 20), with normal scores for the individual domains being ≥ 3.5 (ex 4) [145].

3.4 Performance Measures.

3.4.1 Steer Clear.

This is a vigilance test developed to be a driving related performance measure. It is not a driving simulator. It comprises a computer based monotonous task of avoiding obstacles (cows), on a two-lane road, pressing the space bar on the computer to

change lanes and therefore avoid the cow. It is run for 30 minutes and the cows intermittently appear in either lane, and for three 2-minute periods during the test there are no cows to increase boredom. The score is expressed as a percentage of cows hit, therefore the lower the score the more vigilant the subject.

Normative data was assimilated by Findlay et al who designed this vigilance test, from age and sex matched controls in included in their studies [174]. They report a normal score as < 1.8% obstacles hit, a poor score as >1.8% but ≤ 4.5 % obstacles hit and a very poor score as > 4.5% obstacles hit. Examples of steer clear results for a sleepy patient and the same patient after a month of CPAP therapy are included in appendix 1.

3.5 Cognitive Function.

3.5.1 Digit Span.

This is a test from the Wechsler batteries [483,484], and is one of the most commonly used test of short-term memory, reflecting the span of immediate recall. This test allows two trials at each span length [485].

This test comprises two different tests; digits forward and digits backward, which involve different mental activities that could be affected differently. Each test contains seven pairs of random number sequences, each pair being different. Each string of numbers is read aloud at one digit per second, and therefore attention skills and short-term memory are tested. The overall score is calculated by combining both the forward and backward scores with the participant gaining a point for each string

of numbers that they recall correctly. The test has some limitations with the pooling of the forward and backward data, as it could mask differences in brain dysfunction as the overall score would not reflect a large difference in the forward and backward scores and therefore may underestimate a degree of brain dysfunction [486]. Therefore to gain the most meaningful information the data in this study has been left in the 'forward' and 'backward' scores, subtracting forward from backward scores, as well as a global score.

Subjects are given a string of numbers and are asked to repeat them exactly as heard, or in reverse, and the examiner continues until the subject fails both strings of the same length. The 'normal' range for forward scores is 6 ± 1 [486], a score of 4 is borderline and 3 is defective. Anxiety can reduce the number of digits recalled. The normal range of a backward score is 4-5, with 3 being borderline, and 2 defective. These scores can be affected by the patients educational background, and by their age in later life. This has not been taken into account during this study as the patients act as there own control. The format of the test is included in figure 3.2 overleaf.

Figure 3.2: Digit Span.

Discontinue after failure on **both trials** of any item.

Administer **both trials** of any item, even if the subject passes the first trial.

DIGITS FORWARD		Pass/ Fail	Score 2,1 or 0
1	5-8-2 6-9-4		
2	6-4-3-9 7-2-8-6		
3	4-2-7-3-1 7-5-8-3-6		
4	6-1-9-4-7-3 3-9-2-4-8-7		
5	5-9-1-7-4-2-8 4-1-7-9-3-8-6		
6	5-8-1-9-2-6-4-7 3-8-2-9-5-1-7-4		
7	2-7-5-8-6-2-5-8-4 7-1-3-9-4-2-5-6-8		

DIGITS BACKWARD		Pass/ Fail	Score 2,1 or 0
1	2-4 5-8		
2	6-2-9 4-1-5		
3	3-2-7-9 4-9-6-8		
4	1-5-2-6-8 6-1-8-4-3		
5	5-3-9-4-1-8 7-2-4-8-5-6		
6	8-1-2-9-3-6-5 4-7-3-9-1-2-8		
7	9-4-3-7-6-2-5-8 7-2-8-1-9-6-5-8		

3.5.2 Stroop Colour Word Test.

This is a common neuropsychological assessment method, and helps tease out the motor skill aspects of a task. It tests the ease at which a person can shift their perceptual set to cope with changing tasks to perform an unusual task over a habitual one. It is a multi modal test, testing verbal function, executive function, cognitive flexibility, concentration and selective attention. It is based on the finding that it takes longer to call out the colour of printed words rather than read them. It is a measure of concentration, with the ability to register the colour of the word whilst blocking out the reading of the word. There are a number of versions of this test, I used one of the Dodrill formats [139,487], which consisted of 176 colour word names (11 across and 16 lines down) randomly printed in these colours.

The test format used in this study comprised two trials. The first in which the chart is read only, with the words being printed in ink of different colours and the second reading with the same chart, naming the colours of the printed words rather than reading the text itself [488]. The examiners record sheet contains the correct names and these are marked off during the test. The test is included in figure 3.3 overleaf.

Figure3.3: Stroop Colour Word Test.

Red	Blue	Yellow	Green	Blue
Yellow	Red	Blue	Red	Yellow
Blue	Yellow	Red	Yellow	Red
Yellow	Green	Yellow	Green	Green
Red	Blue	Green	Red	Green
Green	Red	Blue	Blue	Yellow
Blue	Yellow	Yellow	Green	Blue
Yellow	Blue	Red	Yellow	Red
Yellow	Red	Blue	Yellow	Blue
Green	Blue	Green	Red	Green
Blue	Green	Yellow	Green	Red
Green	Red	Red	Blue	Green
Red	Yellow	Blue	Green	Yellow
Red	Blue	Yellow	Yellow	Blue
Blue	Red	Green	Red	Yellow
Yellow	Blue	Green	Blue	Green
Red	Green	Blue	Yellow	Red
Green	Red	Yellow	Green	Green
Blue	Green	Red	Red	Yellow
Yellow	Blue	Green	Red	Blue

Scoring is made by time, with the subject being told if they are incorrect during the test and having to correct themselves, therefore taking longer to complete the test. Dodrill evaluated the subjects' performance by looking at the total time to complete the first part and the difference between both parts (part 2 - part 1). It has to be remembered that this test assumes that the patient is able to read and to see the chart, and the patient must not have red/green colour blindness.

Normative data for this form of the test has not been published. This test was constructed to evaluate the difference between the functions of a subject during a trial of some kind. In my study I was looking for a difference between two treatments rather than an absolute value.

3.6 Discussion.

Measuring subjective sleepiness is useful in this study to show improvements with the different treatment modalities and to compare one with the other. Measuring quality of life using the FOSQ is also useful in continuing validation of this very useful sleep specific questionnaire. Utilising tests of neuropsychological function is a complex process with many different tests being available. The different tests can be used to discriminate between the different brain dysfunction's, it is however not desirable in this study to dedicate a large amount of patients time to different tests as these are not central to the main hypothesis and could reduce patient recruitment and retention.

Chapter 4.

Methods of Measurement and Recruitment.

4.1 Body Measurements.

Body length measurements were made using a standard dressmaker's measuring tape. The waist was measured at the umbilicus, the hips were measured at the level of the iliac crests, and the neck was measured at the level of the crico-thyroid membrane. Height was recorded from a standard scale, to allow calculation of body mass index (BMI = weight/height^2). Weight was measured using the standard Sleep Centre scales (Seca, Germany) which are calibrated annually. Measurements are recorded in centimetres (cm) and kilograms (Kg) respectively. Patients were weighted at each visit to ensure that there was no significant change in their weight during the study.

4.2 Nocturnal Polysomnography.

Overnight PSG studies were performed at the Sleep Centre situated in Ward 48 of The Royal Infirmary of Edinburgh. PSG consisted of continuous recording of electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), leg movement sensor, airflow via a thermistor, a microphone for snoring noise, inductance plethysmography for abdominal and respiratory effort, and oxygen saturation using a finger pulse oximeter (Ohmeda 3700e, Colorado, USA). A computerised system is employed to record and store the data utilising a

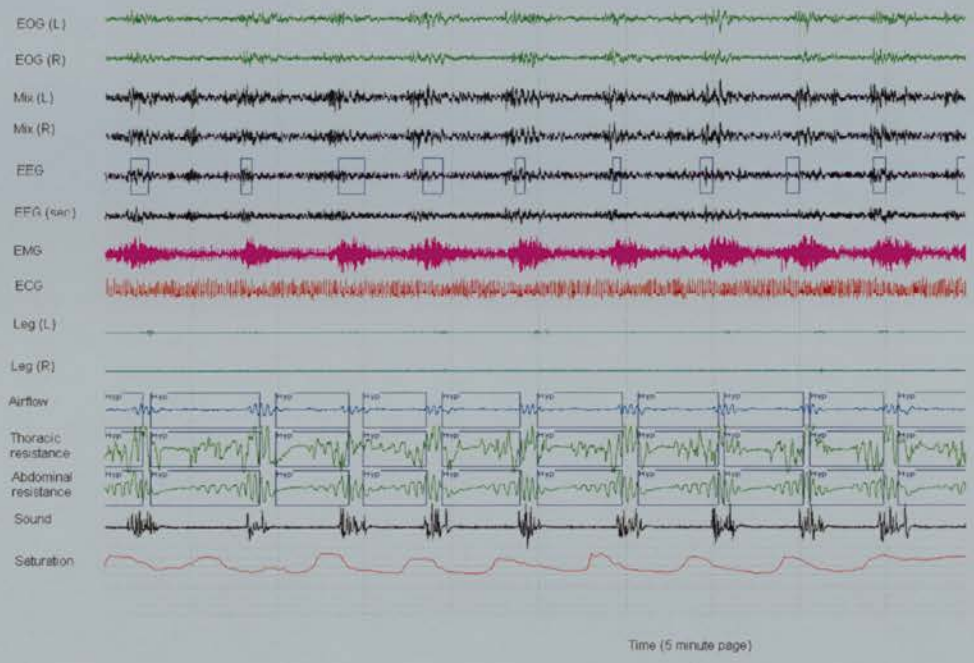
Compumedics package (*S* system, Compumedics, Melbourne, Australia). These data files are backed up onto optical discs.

4.2.1 Sleep Study Scoring.

The trained sleep technicians score all the recordings manually. In house inter-rater reliability testing is performed monthly. Apnoeas are defined as a complete cessation of airflow lasting ≥ 10 seconds [394]. Hypopnoeas are defined as the reduction of at least 50% of the sum amplitude of the thoraco-abdominal inductance signal [19]. Arousals associated with sleep disordered breathing events are defined as an increase in EEG frequency lasting at least 1.5 seconds (Cheshire) with a concomitant rise in EMG activity however brief. Sleep is staged according to the criteria of Rechtschaffen and Kales [489].

Using these criteria, studies were sleep staged along with respiratory and EEG arousals marking to allow formal scoring and the calculation of an apnoea/hypopnoea index (AHI), and an EEG arousal index per hour slept. Sleep efficiency was also reported as a percent of the time asleep against the total available sleep time, to ensure enough time was slept. The nadir in oxygen saturation overnight was reported along with a starting saturation.

Figure 4.1: Typical page of OSAHS.



The hypopnoeas are marked with the boxes in the figure showing the frequent events in this 5-minute exert of a sleep study. The oxygen desaturation is evident on the saturation trace at the bottom of the diagram, the scale of which is 0-100%.

4.2.2 Desaturation Index.

The desaturation index is calculated from the PSG recording. Each PSG trace is reviewed manually and any areas of oxygen saturation artefact edited out. The number of 4 % oxygen desaturations are counted during the total sleep time (wake periods are excluded). This total number is then divided by the total sleep time in

minutes and multiplied by 60, giving the number of events per hour slept, so called the desaturation index (DI).

4.3 CPAP Titration.

This was performed overnight in the Sleep Centre using a computerised system (Auto Set, ResMed, Sydney, Australia), which set the ideal CPAP pressure required to abolish apnoeas, hypopnoeas and flow limitation. Performing the CPAP titration overnight in the centre allows an opportunity to sort out any common mask problems and set the treatment pressure, it was hoped that this would improve compliance. The pressure the CPAP units were set at was usually the 95th centile from the computer printout, i.e. abolishing 95% of events.

4.4 Blood Pressure.

4.4.1 Ambulatory Blood Pressure Monitoring.

The ambulatory BP system, (Ultralite ABPM, 90217, SpaceLabs Medical Ltd., Redmond, WA, USA) is a small lightweight battery powered microprocessor, which stores data collected via an arm cuff. The ABPM measures 2.8 x 11.4 x 8.6cm and weighs 347g. It has on the front panel a four-digit liquid crystal display, a manual start/stop button and attachment for the BP cuff. The rear panel contains a serial communications port and the on/off switch. The data can be transferred to a personal computer via a PC interface for formal analysis and production of a hard copy of the

data. The monitors are carried in pouches, which are worn either with a belt or a shoulder strap.

The monitors can be programmed to various features, displaying cuff pressure at each bleed step, and displaying systolic, diastolic, mean arterial pressure and heart rate at the end of each cuff inflation. They continue to bleed to 40 mmHg rather than stopping at the diastolic value, and although they can bleep before and after each recording is taken, the bleep is disarmed during this study. The machine takes Korotoff sounds one and five for the recordings [490]. The monitor bleeds air in discrete steps (approx. 4 mmHg) using the oscillometric method of BP determination. The monitor measurement ranges are: heart rate 40-180 mmHg; systolic BP 70-280 mmHg; diastolic BP 40-200 mmHg; and mean arterial BP 60-240 mmHg.

The microprocessor can be programmed to take recordings at intervals of 6 to 120 minutes, in our case every 30 minutes. It takes approximately 30-50 seconds to make a recording, and after any failed attempt, the monitor is programmed to try a further recording one-minute later. The cuff pressure inflates to 170 mmHg initially, then to 30 mmHg above the previous systolic recording. The microprocessor is programmed to distinguish between pressure signals, patient movement and respiratory artefact. The pressure transducer channel automatically zeros before taking a recording. The cuff is inflated with an automatic pump, and the bleed rate is also controlled via the microprocessor. The device contains a real time clock, which is recalibrated with each monitor initialisation. The monitor is initialised before being fitted to each patient, this ensures that the time clock is correct and allows the patients identification data to be stored with the collected data. The microprocessor auto-

edits aberrant results. For safety purposes the measurement cycle is limited to 180 seconds, and the absolute maximum pressure of the cuff is 310 mmHg.

The accuracy of BP recordings detected with this device is equivalent to those obtained by a trained observer using a manual cuff method [309,341,490]. The validity and accuracy of ABPM's has been documented [309,341,490-493].

There are two important sources of variation in blood pressure, the biological variation and measurement error variation. The latter needs to be controlled for as much as possible. The ABPM will take recordings in a variety of settings. However because the recording is done automatically it removes observer bias [490,494]. The data produced by these machines has been shown to be reproducible [493,495]. There are several different ambulatory devices available, one study compared 4 of these along with intra-arterial recordings showing that their accuracy is similar at rest but during exercise some of the ambulatory monitors are less suitable. The SpaceLabs device is favourable in this respect as it uses the oscillometric method of recording [491,492,496,497]. There are some concerns with the ambulatory monitors that they may overestimate DBP, however in our case this is not a major issue as such, because the difference between measurements with different treatments is the important outcome in this study. Accurate measurements might not be obtained because of patient movement, incorrect cuff position/size, extreme HR or BP, arrhythmias, vibration or other environmental stimuli, but again using the patient as their own control should minimise the effect of these confounders on the differences sought. Side effects from wearing the device are minimal and include pain, skin irritation, noise, inconvenience, haematoma, and altered sleep quality [498].

Accuracy of the device is checked at least yearly using a full sized mercury sphygmomanometer, a T-tube and a rigid cylinder. The cuff is placed around a rigid cylinder and attached to the ABPM via a T-tube, with the second part of the tubing being attached to the sphygmomanometer. The ABPM is then activated manually and readings compared as the monitor bleeds air stepwise, the readings need to be within 3 mmHg of each other.

Patients were asked to continue with normal daily activities whilst wearing the monitor, and were permitted to remove it for bathing only. Instructions on how to reposition the cuff correctly were also supplied. They were also requested to stop what they were doing when the monitor started to take a reading and ensure their arm is straight, until the cuff deflates once more. Patients were asked to keep an activity diary whist wearing the monitor and to abstain form caffeine containing products during this time also. For statistical analysis data was transferred to Microsoft Excel for further analysis.

A major problem with monitoring blood pressure during sleep is that non-invasive methods can cause an arousal and therefore artificially elevate blood pressure [499,500], although this is thought to lessen over time. Intra-arterial methods are more accurate and do not cause an arousal from sleep per se. However such techniques are invasive and have all the associated risk factors and problems of an intra-arterial line. It would be much more difficult, if not impossible for the patient to conduct normal activities with an arterial line in situ, and would therefore not be an accurate reflection of normal circadian blood pressure.

I decided to accept the imperfect nocturnal blood pressures we would achieve with a cuff technique, realising that it may result in overestimation of the nocturnal blood

pressure but also in minimisation of any decrease in blood pressure at night resulting from CPAP. This could occur because sleep quality would be expected to be better on CPAP and thus blood pressure might be expected to be lower without the arousal related surges in pressure. Measurements with a cuff are possibly made in wakefulness [499]; and in interpreting data from such studies this must not be forgotten as the benefits of CPAP may be minimised. A sample printout for the ABPM is included in Appendix 1.

4.4.1.1.Validity of ABPM Recordings.

It is important to show that the ABPM's give reproducible results, as the BP measurements are the crux of this thesis. Therefore I subjected the units to reliability testing. I recruited 3 subjects from our staff in the sleep centre who volunteered to wear the ABPM's for a 48-hour period. Their data are presented in table 4.1 overleaf.

It is clear to see that the ABPM's provide reproducible results. Co-efficient of variation is calculated as the standard deviation divided by the mean multiplied by 100 so that it is expressed as a percentage.

Table 4.1: Co-efficient of variation of ABPM a measure of validity.

	1st 24-hours	2nd 24-hours	Mean (SD) (day 1 + 2)	Co-efficient of variation (%)
SBP				
Subject 1	131	129	130 (10.5)	8
Subject 2	127	123	125 (11.5)	9
Subject 3	112	110	111 (13.9)	13
DBP				
Subject 1	79	77	78 (9.8)	13
Subject 2	78	82	80 (10.3)	13
Subject 3	69	65	67 (12.3)	18
MAP				
Subject 1	96	94	95 (9.6)	10
Subject 2	94	94	94 (9.8)	10
Subject 3	82	80	81 (12.0)	15
HR				
Subject 1	87	85	86 (7.0)	8
Subject 2	69	69	69 (12.0)	17
Subject 3	68	66	67 (12.6)	19

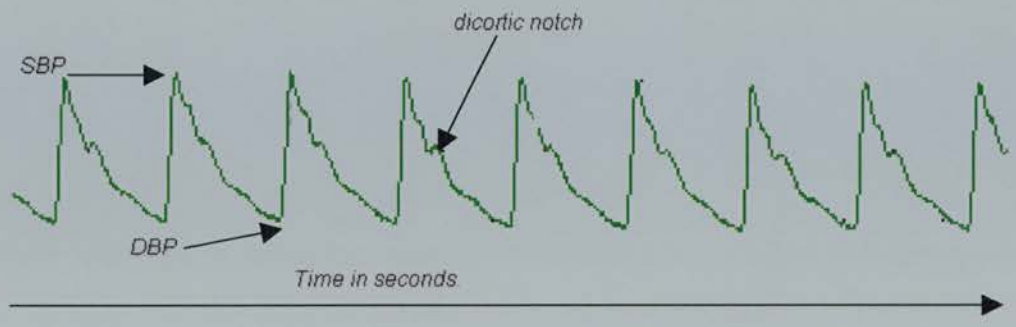
4.4.2 Beat-by-beat Blood Pressure.

The Finapress (Datex-Ohmeda) is a device that measures beat-by-beat blood pressure from a finger cuff. This device depends on a pneumatic servo-controlled cuff, which is inflated to keep the infrared absorption in the finger constant by the correction of a photoplethysmogram. The infrared absorption in the finger alters due to variation in blood volume in the finger, changes in cuff pressure are therefore required to keep the photoplethysmogram constant, which reflects changes in the intra-vascular pressure. It is an accurate method of monitoring short-term changes in BP, and can track the changes that occur during the Valsalva and Müeller manoeuvres, atrial fibrillation and OSAHS. Digital arterial pressure however differs from brachial artery pressure because of the hydrostatic effects of the hand position, and the normal change of the BP along the vascular tree, the plethysmographic volume clamp is best used as an *index of change* in BP rather than of absolute pressure.

The cuff was attached to the middle finger of the left hand, using an appropriate sized cuff. Patients were allowed to acclimatise with all the equipment running, and rested unstimulated for 30-minutes before any recordings were made. The servo-self adjust (in-built calibration mode) was disabled on the Finapress device during each 5 minute test run. It was then reactivated, if there was more than a 5 mmHg difference in the readings the test was re-run. Data for the whole time period was recorded, however the analysis was only performed on the five-minute time blocks. Three sets of recordings, lasting 5 minutes each, were taken for every patient during both visits.

Figure4.2: Example of Finapress Recording:

BP-in mmHg



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4.5 Baroreceptor Reflex Sensitivity.

The assessment of this entity assumes a positive correlation between a stimulus and a response, e.g. change in blood pressure and change in pulse interval (PI). It therefore reflects the ability to alter the vagal activity in relation to the sympathetic activity in a reciprocal manner. It has been previously shown that BRS is diminished in several diseases most notably hypertension (1452).

The patients were asked to abstain from alcohol, smoking and caffeine for the 12 hours prior to attending for the study. All baroreceptor studies were performed between 8am and 1pm. The patients were placed in the supine position in a quiet, dimly lit room and left unstimulated. Electrocardiographic recordings were taken from chest leads in position II. The skin was prepared using an exfoliating gel and

wiped with alcohol before the electrodes were placed to ensure good contact. Beat by beat blood pressure was recorded using the method described above. Data from the ECG and Finapress were recorded on a PC using a special montage in the Compumedics software described previously. Data from these files were backed up onto optical discs.

Figure 4.3: Example of Baroreceptor Recording:

Data were further analysed using a power spectral analysis technique utilising an especially in-house written computer program, which also included the calibration and editing of the stored data. This allowed the calculation of pulse interval (PI), pulse interval power (PIp), and the different low frequency (LF), very low frequency (VLF) and high frequency (HF) bands. It also allowed the calculation of baroreflex sensitivity (BRS), and allows the calculation of the ratios of BRS LF/HF, and LF/HF PIp.

Patients underwent this study at the end of each treatment limb before crossing over onto the alternative treatment. Data were further analysed using the SPSS statistical program to compare the different treatments.

Power spectral analysis was also performed on the beat to beat BP and PI, the signals being transformed into the frequency domain with a fast Fourier transform algorithm as discussed in section 2.7.6.

4.6 Epworth Sleepiness Score.

This subjective sleepiness questionnaire previously discussed in Chapter 3 was given to the patients who were asked to give themselves scores from 0-3 in eight different situations, giving a maximum score out of 24. They complete the questionnaire when alone and were asked to refer to their performance in the previous month. It was completed at the start of the study before the CPAP titration to allow familiarisation and at then end of each treatment limb.

4.7 Functional Outcomes of Sleep Questionnaire.

Patients were asked to complete this 26-question survey based on how they had been feeling in the previous month. They were alone whilst completing the task. The FOSQ was completed at the start of the study to allow familiarisation and at the end of each treatment limb.

4.8 Steer Clear.

The patient was placed in front of a computer screen in a quiet darkened room to perform the steer clear test as described in chapter 3. The computer screen was blank; the patient needed to press the spacebar with the dominant hand to commence the test. This test ran for thirty minutes, and terminated automatically. This test was also performed at the start of the study to allow familiarisation and at the end of each treatment limb.

4.9 Digit Span.

This was a further test of concentration and mental dexterity as described in chapter 3. Patients were told that some numbers would be said to them and they would be asked to repeat them back, initially forwards, then later in the test backwards, and that the string of numbers would get progressively longer. The patients were given an example to illustrate the test. Patients completed this test at the start of the study to allow familiarisation and at the end of each treatment limb.

4.10 Stroop Colour Word Test.

The patient was given a card with a copy of the Stroop test on it (Figure 3.4). Patients were then asked to read the card on two occasions, the first time to read the words going left to right across the page as if reading a paragraph in a book, then name the colours the words are printed in. This test was run at the start of the study to allow familiarisation and at the end of each treatment limb.

4.11 Urinary Microalbumin.

This was measured from a spot urine sample collected from the patients at their first study visit to the centre. The sample was sent to the Biochemistry Laboratory of the Royal Infirmary of Edinburgh who performed a radioimmunoassay to determine the concentration of albumin and creatinine in the sample so that a ratio of albumin to creatinine excretion can be derived. This will be discussed further in chapter 9.

4.12 Recruitment.

Consecutive patients who attended the Sleep Centre at Edinburgh Royal Infirmary meeting the inclusion criteria were approached. Patients were contacted in person in the centre, or by telephone, explaining the objectives of the study and what was involved. If patients agree to participate they were then given an information sheet on the study (appendix 1), and a date to come back for the CPAP titration study.

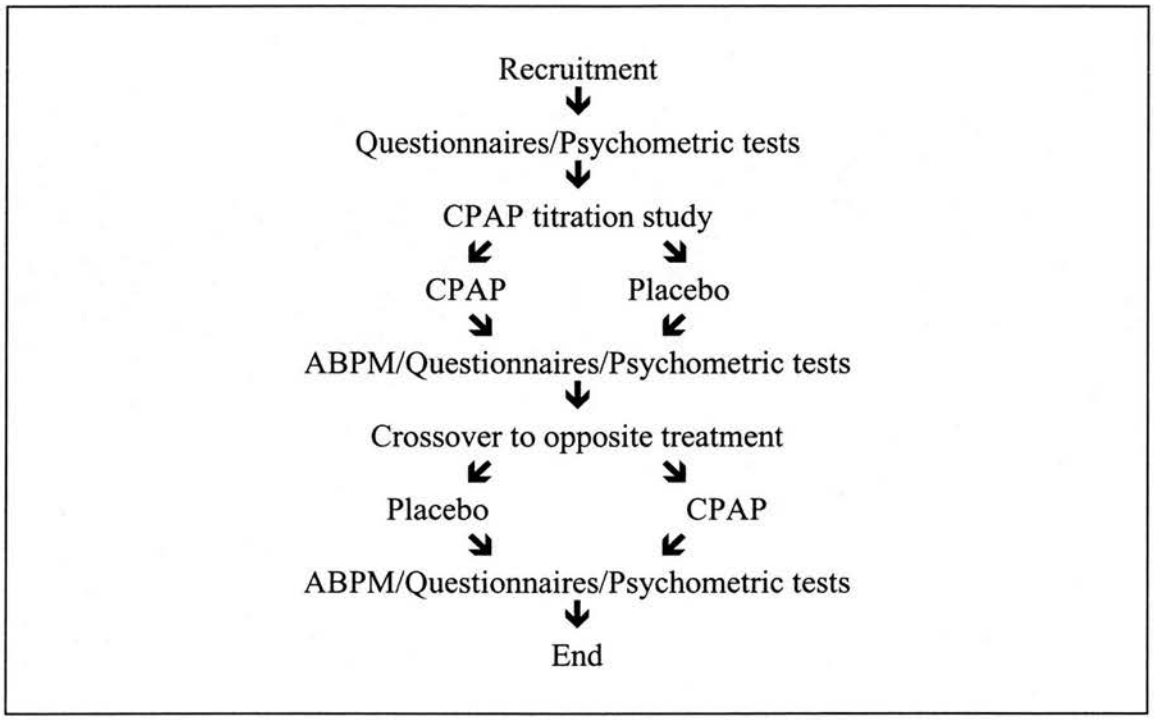
Patients told that the study was to compare two different potential treatments for OSAHS, one established and one new. They were told that the capsules may affect upper airway tone and therefore reduce the number of breathing pauses, they were informed that some patients had done well with the medication, and others had not felt the medication had helped at all. Patients were also informed that we wanted to look at the effects of both treatments on their blood pressure. The placebo was actively sold to our patients as a possible active treatment. This had ethical approval.

Table 4.2 Recruitment Criteria.

Inclusion Criteria
AHI ≥ 15 events per hour slept
Two major symptoms of OSAHS [501]
Between the ages of 20 and 80 years
Exclusion Criteria
> 50 miles from the sleep centre
Taking any medication which affects blood pressure
Any disorder which affects blood pressure e.g. diabetes
Had fallen asleep at the wheel within the last 5 years

Once patients agreed to participate in the study and provide written informed consent, they were invited to a CPAP education session followed by a CPAP titration study. The education session comprised viewing a video about OSAHS and CPAP followed by a mask fitting with our specialist nursing staff or technicians, ending with a 30-minute trial of CPAP. The patients attended for their overnight CPAP titration and they were asked to complete the ESS, and FOSQ. Weight was recorded and the measurements are taken as previously discussed. Patients were then acclimatised to Stroop, Digit Span and Steer Clear tests.

Figure 4.4: Study Design.



The CPAP titration study was performed overnight using the automated AutoSet system. The morning following the CPAP study the patients were randomised into the study, randomisation is performed using a balanced block design with four patients per block. Randomisation allowed half of patients to start with CPAP and half to start with the oral placebo.

Once randomised patients received CPAP or the placebo for a month, at the end of each month block they attended the Sleep Centre and completed ESS and FOSQ questionnaires, performed psychometric testing and had the ABPM fitted. The ABPM was worn for 48-hours during which the current treatment was continued. The ABPM was then collected from the patient's home and the treatment for the next month issued. Patients were contacted by telephone at least twice during each

treatment limb and a home visit was performed if necessary. At the end of the study all patients had CPAP therapy offered. Patients were given contact telephone numbers for the Sleep Centre, in case of any problem during the study. The patient's general practitioners were also kept fully informed by letter regarding their patient's participation in the study with contact details in case of any problems or concerns. Included in this information was a sealed envelope containing details of the oral placebo in case of an emergency.

4.13 Data Analysis.

Data for all 68 patients were entered into a large data base using Microsoft Excel. Data were analysed using a variety of statistical tests on a PC statistics package (SPSS for windows, Version 10, 1999, SPSS, Chicago, IL, USA).

4.13.1 Blood Pressure Data.

The data were normally distributed. The blood pressure equipment provides a result for each 30-minute time point, resulting in a huge number of data entries for each perameter; SBP, DBP, MAP, HR and PP. I was concerned that with this number of data points significant findings may be found as a result of chance. Therefore the data was grouped into 4 hourly means at the advice of the Professor of Medical Statistics, after which a repeated measures general linear model was used, which allowed me to take into account the order to ensure there was no order effect, and to enter all the results. All data were analysed on an intention to treat basis. Missing data points were filled in using imputation, this affected < 1% of results. Data were

blinded to me prior to imputation, by anonymising and batching, and prior to formal statistical analysis being performed.

Prior to data analysis two *a priori* end points were chosen, CPAP use ≥ 3.5 hours a night, a figure chosen based on previous work from our sleep centre. Furthermore a desaturation index of ≥ 20 was chosen as the second *a priori* end point, looking at a more severe group of patients. The decision to look at patients who desaturated more was based on the work done by Brooks [388]. In the dog model of OSAHS, they showed that dogs who desaturated developed sustained daytime hypertension, compared to the dogs who only has their sleep fragmented without hypoxia being induced.

4.13.2 Baroreceptor Data.

The data collected from this sub study is outlined in section 4.10. These data were normally distributed. The results of the spectral analysis were analysed using the MANOVA. The two treatment modalities are compared.

4.13.3 Psychometric Tests.

These data were differently distributed, both the Steer clear and Stroop colour word test were asymmetrically distributed therefore non-parametric Wilcoxon tests were utilised. Digit span was normally distributed and therefore the MANOVA was employed in further analysis.

4.13.4 Quality of Life Questionnaires.

These data were normally distributed and were analysed using a MANOVA taking order into account to ensure there was no order effect of the treatments.

4.14 Patient Group.

One hundred and seven consecutive patients were approached to participate in this study, 78 patients agreed to participate. Prior to commencement in the study 7 patients withdrew for a variety of work and personal commitments. Seventy-one patients started the study, 3 were lost during the study one during the placebo limb and two during the CPAP limb. In total 68 patients completed the study. It is the data from these 68 patients, which will be included in the next three chapters. Two smaller subsets of this main group were further studied looking at baroreceptor function (chapter 8) and urinary microalbumin (chapter 9), details of these groups are included in the relevant chapter.

4.14.1 Demographics.

The demographics of the patients who completed the study are included in table 4.3 below.

Table 4.3: Demographics of Study Population.

	Mean	SEM	Range
Age(years)	49	1.2	27-72
AHI (/hr slept)	44	3.4	15-129
EEG arousals (/hr slept)	48	2.9	12-129
4% Desaturation Index (/hr slept)	16	2.8	0-128
BMI (Kg/m^2)	31	0.8	21-55
Neck (cm)	41	0.5	33-55
Waist (cm)	105	1.8	76-155
Hips (cm)	109	1.5	93-160

Demographics of the sub-populations studied are included in the relevant chapters.

Chapter 5.

Blood Pressure Results.

5.1 Introduction.

Of the sixty-eight patients who completed this study, 55 were male and 13 female.

5.2 Statistics.

Statistical analysis is performed as described in section 4.13.

5.3 Results.

5.3.1 Intention to Treat Results.

The results of analysis of the mean 24-hour BP from all data sets irrespective of compliance with therapy are shown (table 5.1).

Table 5.1: Mean Blood Pressure for Study Cohort.

	CPAP		Placebo		P-value
	Mean	**SEM**	**Mean**	**SEM**	
SBP (mmHg)	126.9	1.3	128.2	1.2	0.19
DBP (mmHg)	77.8	1.0	79.2	0.9	**0.04**
MAP (mmHg)	94.4	1.0	95.5	0.9	0.20
HR (bpm)	76.2	1.1	76.8	1.1	0.43
PP	49.3	0.9	49.1	0.9	0.78

DBP is the only significant variable changed by CPAP therapy when analysing the full 24-hour data. I then examined the different times of day to see if these DBP changes are more marked at any specific time of day or night. As part of the statistical analysis for the general linear model all the data points were grouped into 4-hourly means, using these time blocks the data are compared in table 5.2 below.

Table 5.2: Mean DBP in 4-hour Time Blocks.

Time block	CPAP		Placebo		p-value
	Mean	SEM	Mean	SEM	
18.00-21.59h	80.9	1.2	82.3	1.2	0.24
22.00-01.59h	73.6	1.1	74.5	1.2	0.43
02.00-05.59h	67.9	1.2	69.8	1.1	**0.03**
06.00-09.59h	75.5	1.3	78.5	1.3	**0.02**
10.00-13.59h	83.6	1.3	84.9	1.3	0.34
14.00-17.59h	84.3	1.1	85.3	1.2	0.41

The main change in the DBP in the 24-hour period is between 02.00h and 09.59h. The average wake time reported by the patients during the study was 7 a.m. (range 04.45 - 11.00 h) and so the 06.00 to 09.59 block contains a significant portion of wake time.

5.3.2 CPAP use ≥ 3.5 hours night.

32 patients used their CPAP ≥ 3.5 hours per night and a sub analysis is done on their data and the results are included in table 5.3 below.

Table 5.3: Mean BP of Patients Who Used CPAP ≥ 3.5 hours Per Night.

	CPAP		Placebo		P value
	Mean	**SEM**	**Mean**	**SEM**	
SBP (mmHg)	129.9	2.1	131.0	1.8	0.41
DBP (mmHg)	79.6	1.2	81.5	1.2	**0.03**
MAP (mmHg)	96.6	1.4	97.7	1.2	0.30
HR (bpm)	76.3	1.7	76.6	1.6	0.78
PP	50.3	1.6	49.5	1.5	0.31

DBP is significantly reduced with CPAP treatment compared to oral placebo in these better CPAP users, and the magnitude of the change is marginally greater in this group (mean 1.9 v 1.4 mmHg).

5.3.3 Desaturation Index ≥ 20 events Per Hour Slept.

The second a priori group included those patients with a desaturation index ≥ 20 events per hour slept, and 14 patients fulfilled this criteria. Their data are sub analysed (Table 5.4).

Table 5.4: Mean BP of Patients With a Desaturation Index ≥ 20 events Per Hour Slept.

	CPAP		Placebo		P value
	Mean	SEM	Mean	SEM	
SBP	129.1	2.1	133.1	2.8	**0.009**
DBP	77.4	2.1	82.4	2.1	**0.002**
MAP	95.2	1.8	98.6	1.9	**0.012**
HR	78.0	3.2	76.7	3.3	0.626
PP	51.7	2.4	51.0	2.5	0.418

Post hoc, I examined a less severe group of patients with a desaturation index of ≥ 10 4% desaturation's per hour slept to see if this decrease in SBP, DBP and MAP is sustained. Their data are included in table 5.5 below, and includes 30 patients.

Table 5.5: Mean BP of Patients With a Desaturation Index ≥ 10 events Per Hour Slept.

	CPAP		Placebo		P value
	Mean	SEM	Mean	SEM	
SBP	127.3	1.9	130.5	1.8	**0.015**
DBP	76.8	1.4	80.5	1.3	**0.001**
MAP	94.1	1.3	96.9	1.2	**0.014**
HR	77.4	1.8	76.5	1.7	0.543
PP	50.3	1.7	50.4	1.6	0.882

These patients who desaturated less than the *a priori* group have significantly lower SBP, DBP and MAP with CPAP therapy compared to oral placebo. Even though these data include some patients who are less than compliant, CPAP use 3.5 hours/night (range 0.1 – 8.1 hours/night), a significant drop in SBP, DBP and MAP is seen.

5.4 Discussion.

This study shows that DBP is significantly reduced in patients with CPAP therapy, although the mean drop is small (1.4 mmHg). However looking at the compliant patients with a CPAP use ≥ 3.5 hours/night, the drop in DBP elicited is greater (1.9 mmHg). One of the main findings of the study is that nocturnal hypoxaemia is a key determinant of the decrement in blood pressure with CPAP therapy. Both in the *a priori* severely hypoxaemic group and in the less hypoxaemic *post-hoc* group, the SBP, DBP and MAP are all significantly reduced.

OSAHS undeniably causes transient rises in nocturnal BP, leading to an elevated sleeping MAP [87]. Transient post apnoeic rises can be as much as 100mmHg, at least partly due to the repetitive arousal from sleep. BP lability makes the interpretation of the night-time BP recordings in non-OSAHS patients using inflating cuff techniques difficult, partly because they are set up to take interval BP rather than continuous BP, and they do not record the acute swings in BP seen in this patient group. There is also considerable debate in the literature about the effect of ABPM's on sleep quality, and whether they can lead to awakening from sleep [499,502,503] or not [504], partially because of the pressure of the cuff on the arm and partially from the noise of the

motor unit. If the device does cause awakening from sleep this in turn may elevate the BP [499,500] or not [502,503]. However acclimatisation does occur [482]. This type of monitoring device is being more frequently employed in sleep research to examine the effect of the disorder on BP.

This study performs recordings over a 48-hour period in an attempt to minimalise the affects of the ABPM on BP and sleep quality. The other thing that must be remembered with these ambulatory BP devices is that they can cause awakening from sleep. This awakening can affect the BP, it may also have an impact on sleep fragmentation, which in turn may affect any test results done on the day following wearing the device overnight [193,482].

Some studies have also examined the BP changes (associated with the different stages of sleep) in relation to SDB events. Davies et al [87] performed a study looking at BP changes in OSAHS, quantifying the severity of OSAHS by the number of oxygen desaturations > 4%. They looked at two periods of ten minutes each overnight, with the same body position, looking at NREM sleep periods only. The mean values were averaged over the twenty minutes. However three of the 18 OSAHS patients were taking anti-hypertensive medication, as were two of the 16 snorers and one of the 34 controls. The study shows that there was a significant increase in BP in the patients with OSAHS compared to controls. They also demonstrated that the resting pre-sleep BP was elevated in the OSAHS group compared to matched controls.

Davies et al reported a further study looking at 24-hour BP in 6 normal subjects to see if the ABPM's caused an arousal from sleep and any change in beat by beat BP [499]. Each subject was studied twice, at least 2 weeks apart with the different ABPM's,

with 30-minute interval BP recordings. During the sleep time the patients also had a Finapress device fitted on the opposite arm to the ABPM, to record beat-by-beat BP. EEG recordings were also taken to allow sleep to be staged and arousals to be identified. The duration of each arousal from sleep that was due to the ABPM cuff inflation was noted. The Finapress recordings were taken after no hand movement was observed for 60 seconds after the cuff has started to inflate, and six periods of 10 seconds were recorded. The effect of the rise in BP due to the ABPM from the start of inflation to the result being displayed was demonstrated with the Finapress. They demonstrated that both ABPM devices caused arousal from sleep with mean arousal lengths of 8 and 16 seconds for the two machines. Some cuff inflation's were shown not to cause any EEG arousal, and the average duration of arousal reduced as the sleep deepened. They also showed that BP increased even if there was no demonstrated EEG arousal with the cuff inflation. Interestingly they showed that mean DBP remained on average unchanged, but mean SBP was elevated which may suggest that perhaps the SBP measured in my study be artificially high, and possibly confound the results further. They argue that the time to take DBP recordings was longer therefore it has longer to return to 'normal' as the patient returns to sleep. Therefore SBP was probably overestimated during "sleep" using an ABPM, and BP varies during the different stages of sleep and among individuals. This study looked at the Oxford Medical ABP and the A&D TM2420 which were different from the SpaceLab device I employed, however the length of measurement cycles are comparable at approximately 60 seconds. But the study did not comment on daytime recordings. Transient auditory and tactile stimuli in sleep have been shown to increase BP briefly even if no EEG arousal is seen [364].

Davies et al [472] using a group of very carefully matched controls, looked at 24-hour BP profiles in 18 men with severe OSAHS, and their LV mass. This was one of the first studies to have tightly matched controls and shows an increase in BP in patients with OSAHS in NREM sleep compared to the pre sleep wake BP. The blood pressure changes of OSAHS are very rapid therefore they are not suited to intermittent cuff measurement, however the ABPM's can be used to give average BP's and the trend in BP. This study however only looked at a very small time window compared to the whole night, all in NREM sleep. The severity of the OSAHS was not included, nor the impact of apnoeas or hypopnoeas on the recording. There is also some concern that ABPM's can cause arousals, halting the apnoea or hypopnoea and therefore change the sleep BP profile, but if anything it could underestimate the change by reducing the severity of the length of the apnoea or hypopnoea. This study also looked at the daytime blood pressure using ABPM, [472], and did not demonstrate any differences in the daytime BP in their patient groups. In addition some of their study population were taking anti-hypertensive medication.

My data combined with recent epidemiological data indicates that OSAHS can elevate BP. This adds to the already long list of consequences of OSAHS and reinforces the need for OSAHS to be considered an important medical disorder. However it is not clear at what threshold of AHI significant cardiovascular consequences occur. Patients with an AHI $\geq$ 15 events/hour or >10 4% desaturations/hour are usually offered treatment if symptomatic and this is backed by evidence from randomised controlled trials [236,238,240].

There is evidence of improvement in health status achieved by treating symptomatic patients with an AHI between 5-15 events/hour [239]. What then is the current threshold

for treatment? The objective data for symptomatic patients indicates those with more than 5 events/hr can benefit from treatment in the short term. However longer term study indicates that half of the patients with 5-15 events per hour will quit CPAP within 3 years [229], thus long-term benefit may not be achieved in all these patients with currently available therapy.

There is at present no evidence of benefit from treating asymptomatic patients with frequent apnoeas and hypopnoeas [244]. The current study demonstrates a reduction in blood pressure with CPAP in symptomatic OSAHS patients and cannot be extrapolated to asymptomatic subjects. Further randomised-controlled studies are needed in such individuals.

Oxygen desaturation was thought to be important in the pathogenesis of the transient BP changes during sleep in OSAHS. Ringler et al [233] studied blood pressure response in patients with obstructive sleep apnoea, with and without supplemental oxygen to abolish the hypoxia associated with the apnoea, and a blood pressure rise was still recorded. This suggested there were additional factors involved in its pathogenesis, and the hypoxia alone did not explain all the events. This was supported by work from Fletcher who studied hypoxia in rats [461]. However when oxygen is given to OSAHS patients to prevent the hypoxia, the BP profile seems to be unchanged [363,470]. It is clear from the canine model that the hypoxaemia is necessary to see the alterations in BP, and my data would suggest this is also the case in humans.

Chapter 6.

Health Status Results.

6.1 Introduction.

Health status has been previously discussed at length. It was measured in this study to see if there were benefits to my treatment groups as previously reported in the literature. It was measured using two subjective questionnaires, the ESS and the FOSQ. The data collected is presented in tables 6.1 and 6.2 below.

6.2 Study Subjects.

68 patients completed the study, their data are included in this chapter.

6.3 Statistical Analysis.

The data were analysed using a MANOVA as described in chapter 4 as they are normally distributed.

6.4 Results.

6.4.1 Epworth Sleepiness Score.

Using this standard subjective sleepiness score, the results included in table 6.1 were obtained. There is no order effect ($p = 0.321$).

Table 6.1: ESS and Partner ESS Scores.

	Baseline		CPAP		Placebo		CPAP v Placebo p-value
	Mean	SEM	Mean	SEM	Mean	SEM	
Patient ESS (ex 24)	15	0.6	10.	0.7	13	0.8	**0.001**
Partner ESS (ex 24)	14	0.7	11	0.7	13	0.8	**<0.001**

6.4.1 Conclusion.

CPAP improved both the patient's and their partner's interpretation of their ESS scores. The placebo also showed a significant improvement in ESS scores of the patient ($p < 0.001$) but not in the partner's estimation ($p = 0.109$). This is possibly a reflection of a combination of the placebo effect, the desire to help in the project, and the hope of improvement with the medication, it also may reflect the patients desire to take a capsule rather than use CPAP. It also shows that when a partner is available for corroboration their assessment is very valid. It must also be noted that the ESS did not return to 'normal' values (usually taken as < 10), with CPAP treatment, I suspect this is a reflection in the low compliance with CPAP.

6.5 Functional Outcomes of Sleep Questionnaire.

CPAP improves the sleep specific health status (table 6.2).

Table 6.2: FOSQ Scores Pre-treatment, on Placebo and on CPAP.

Domain	Baseline		CPAP		Placebo		CPAP v Placebo p-value
	Mean	SEM	Mean	SEM	Mean	SEM	
GP (ex 4)	3.0	0.1	3.3	0.1	3.2	0.1	*0.070*
SO (ex 4)	2.8	0.1	3.3	0.1	3.1	0.1	**0.010**
AL (ex 4)	2.6	0.1	3.0	0.1	2.8	0.1	**0.004**
V (ex 4)	2.4	0.1	2.9	0.1	2.7	0.1	**0.029**
Total (ex 16)	11	0.4	13	0.4	11.6	0.3	**0.010**

Key to FOSQ subscales: *GP- general productivity*
SO- social outcomes
AL- activity level
V - vitality

6.5.1 Conclusion.

It is clear to see from these results all domains with the exception of general productivity are significantly improved in patients treated with CPAP. This is in keeping with previous reports in the literature [145,159]. It also shows that the placebo effect is strong with the placebo being better than baseline levels. However this is outweighed by the significant improvement with CPAP compared to placebo. There is no order effect ($p = 0.287$).

6.6 Discussion.

Health status is an important area, it reflects a person's well being, and is an indicator of the impact of a disorder on life, both physically and emotionally. The use of standardised questionnaires has made it easier to see the impact on QoL in the research setting comparing two different treatment modalities and also allows comparison between different studies, and between different disorders. In this study I chose only the ESS and the FOSQ, which are both sleep specific. However in retrospect it may have been useful to have also included a general measure such as the SF-36, to allow easy comparison with other common disorders where there has been good evidence on the impact of the diseases on quality of life. I was aware of the amount of time and paperwork the study demanded of the patients and felt that this extra questionnaire might overload them, especially as there are other data on the effect of CPAP on SF36 [158,159].

Chapter 7.

Psychometric Testing Results.

7.1 Introduction.

Psychometric testing was included in the study to show the effects of treatments on vigilance and cognition, and to see if this study agreed with the previous literature.

7.2 Study Group.

The data included in this chapter refers to the 68 patients who completed the study, demographics of which are included in section 4.14.

7.3 Statistical Analysis.

All data were analysed as described in section 4.13 utilising a MANOVA for the normally distributed data and the non-parametric Wilcoxon, for the data which was not normally distributed.

7.4 Results.

7.4.1 Digit Span.

Utilising the digit span test as previously described in chapters 3 and 4, the results are listed in table 7.1 below. This table includes data from the test run at baseline, and at the end of the placebo and CPAP limbs. The data are normally distributed.

Table 7.1: Digit Span Results Pre-treatment, on Placebo and on CPAP.

	Baseline		CPAP		Placebo		CPAP v Placebo p-value
	Mean	SEM	Mean	SEM	Mean	SEM	
Forward (ex 14)	8.0	0.2	8.3	0.3	8.3	0.2	0.736
Back (ex 14)	6.1	0.3	6.9	0.3	6.5	0.3	**0.040**
f-b	1.8	0.2	1.5	0.3	1.8	0.2	0.213
Global Score (ex 28)	14.2	0.4	15.4	0.5	14.9	0.5	*0.095*

f-b – forward minus backward scores

7.4.1.1 Conclusion.

There are no differences in the global digit span scores for the CPAP versus oral placebo, which differs from previous literature [4,505], although there is a trend in the global score. Recent work from Bardwell did not show any significant difference after a week of CPAP [139]. He studied 36 patients, allocating in a randomised manner

to either CPAP or placebo CPAP, the treatment period before restudy was relatively short, and CPAP compliance was objectively measured.

However on looking at the two components of the test, there is a significant improvement in the CPAP versus placebo in the backward score, but this difference is very small. It is surprising that there is such a significant improvement comparing baseline with placebo (global score baseline v placebo $p = 0.006$), but no order effect is present ($p = 0.44$). It should be noted that the mean scores are within the normal range for this test, and therefore perhaps the patients are little affected in this domain and thus it is difficult to elicit a difference.

7.4.2 Steer Clear.

Performance on this vigilance test is not significantly better on CPAP compared to placebo (table 7.2). This table includes data collected from baseline, and at the end of each treatment limb of CPAP and oral placebo. The data are not normally distributed therefore non-parametric tests are used for analysis.

Table 7.2: Steer Clear Results at Baseline, on Placebo and on CPAP.

	Baseline		CPAP		Placebo		CPAP v Placebo P-value
	Mean	SEM	Mean	SEM	Mean	SEM	
% hit	10.9	1.5	7.1	1.3	7.7	1.3	0.322

7.4.2.1 Conclusion.

This test shows a significant improvement in score in patients on placebo compared to baseline ($p < 0.001$), however no significant difference is elicited between CPAP and placebo. There is no order effect ($p = 0.15$).

Previous literature has provided conflicting results, with some showing an improvement in Steer Clear performance [168,477], and some not [136]. Findley studied 12 OSAHS patients against 12 matched controls and showed that the OSAHS patients hit more obstacles in the test, and when 6 of them went onto CPAP for at least 3 months, they reduced the number of obstacles hit significantly [168]. This was a small study, taking a population from their sleep clinic, the OSAHS patients were a more severe group compared to my population (mean AHI 83 v 44/hour slept), there was no placebo arm included nor was the control group studied a second time. The number of obstacles hit in the untreated group was similar to my population (% hit 6.0 v 7.7), there was no comment whether his study population was familiarised with the test, and the big change may be in part a learning effect. CPAP compliance was not included, so the improvement in score may just reflect a learning effect if the patients were non-compliant.

In a prospective study by Kingshott et al, 62 OSAHS patients were studied at baseline and after 6 months of CPAP therapy. The severity of OSAHS was more severe than my cohort with a mean AHI of 62 v 44/hour slept. A highly significant improvement in Steer Clear hits was reported. CPAP use was objectively measured (mean use 4.8 hours/night), however their study was not a RCT.

A prospective randomised single blind, placebo controlled, crossover trial of CPAP versus an oral placebo with one months treatment limbs did not show any significant change in Steer Clear hit rate [136]. The study exposed the subject to the test at baseline to allow familiarisation then at the end of each treatment limb. The study included 23 patients, and CPAP use was objectively reported at 3.2 hours night. The severity of the OSAHS was similar to my cohort at and AHI of 43 v 44 /hour slept.

I think one of the reasons my study did not show any improvement in Steer Clear hit rate was partially that compared to the two positive studies my patient group was less severe. I also studied the patients after a month; the two positive studies were not studied until at least 3 months therapy, however I attempted to allow for familiarisation, which these two studies did not.

7.4.3 Stroop Colour Word Test.

Stroop results (table 7.3 below) are no different with CPAP compared to placebo. The results are not normally distributed; therefore Wilcoxon non-parametric tests are used.

Table 7.3: Stroop Scores at Baseline, on Placebo and on CPAP.

	Baseline		CPAP		Placebo		CPAP v Placebo p-value
	Mean	SEM	Mean	SEM	Mean	SEM	
Read (sec)	61.0	3.3	56.4	1.8	58.4	2.4	0.589
Colour (sec)	132.8	4.6	114.6	3.9	113.2	3.7	0.184
Diff (sec)	71.7	3.7	58.2	2.9	54.8	2.6	0.249

Diff – difference between colour and read times.

7.4.3.1 Conclusion.

Using the Stroop colour word test I found no significant difference between the times on and off CPAP, there is no order effect ($p = 0.482$). One other study using the Stroop test showed significant impairment compared to matched controls, however they had a small sample of 17 in each group, and used a slightly different format of the test [143]. In a more recent study, Bardwell did not show any significant improvement in the Stroop test after a week of CPAP in their randomised-controlled study of 36 patients [139]. A different format of the test was also used, and the treatment duration before re-testing was relatively short. Educational level is

important in this test and it was matched for in Naëgelé's study, that was not necessary in my cohort as the patients act as their own controls.

7.5 Discussion.

The subject of neuropsychological dysfunction has been extensively studied in OSAHS, the importance of providing good quality results cannot be over emphasised using the basis of large randomised controlled studied to provide the most robust data. Utilising the correct test is important, as there are a huge number of different tests available, testing a variety of parameters. The data obtained from my study did not show any significant improvements with CPAP compared to oral placebo except in the backwards digit span test. These results are in agreement to some previous work and contradictory to others, the reasons for this are not clear, however some of the possible conclusions have been discussed above. The other possible reason for the differences reported in the literature and this study may reflect the time of day that the testing was performed. Within this study I tried as much as possible to perform the neuropsychological testing at the same time of day for all patients and to be consistent with each patient. The data included in this thesis comes from a randomised-controlled trial, and therefore provides a high level of evidence.

Chapter 8.

Baroreceptor Sensitivity.

8.1 Introduction.

The long-term consequences of OSAHS remain controversial. The mechanism of changes in nocturnal blood pressure remains a source for debate, as does the mechanism for impact on daytime BP. There has been data suggesting the role of sympathetic modulation in this process [303,304,455,506]. I therefore wanted to explore this concept further within the context of my existing study.

The last 22 patients who were recruited into the main study were also asked to participate in an additional experiment designed to reflect sympathetic tone and baroreflex sensitivity. This study required an extra 2 hours of the patient's time on 2 separate days at the end of each treatment limb and 14 of the 22 patients agreed to take part. One set of data was incomplete due to technical difficulties on the day of measurement, therefore 13 complete sets of data were collected. The patient group was no different from the main study population.

The patients had baroreceptor function assessed both on CPAP and placebo by spectral analysis of heart rate and using beat-by-beat BP as described in Sections 4.4 and 4.5.

8.2 Demographics.

The demographics of this cohort are included in table 8.1; 12 of the 13 subjects were male, and 7 patients had CPAP first and 6 had placebo first.

Table 8.1: Demographics of patients Taking Part in The Sympathetic Study.

	Mean	SEM	range
Age (years)	45	3.2	27-63
AHI/hr slept	55	11	17-129
EEG arousals/ hr slept	57	8.0	22-128
4% DI/hour slept	24	8.3	1-93
ESS (ex 24)	14	1.3	9-24
Partner ESS (ex 24)	15	1.2	7-24
BMI (Kg/m^2)	31	2.3	23-55
Neck (cm)	41	0.9	37-46
Waist (cm)	109	4.5	95-155
Hips (cm)	110	4.3	100-155

8.3 24-hour Blood Pressure Results for This Sub-group.

There are no significant differences in BP on CPAP compared to oral placebo (table 8.2). This may reflect the small sample size with this part of the study, and therefore been underpowered. CPAP use within this group was good at 4.5 hours/night (SEM 0.7).

Table 8.2: Mean 24-hour BP Values for BRS Cohort.

	CPAP		Placebo		CPAP v placebo P-value
	Mean	SEM	Mean	SEM	
SBP	127.9	2.9	127.1	2.6	0.65
DBP	78.2	1.7	79.0	1.8	0.59
MAP	95.0	2.1	94.3	1.7	0.72
HR	76.8	2.9	76.5	2.3	0.63
PP	49.6	2.0	48.1	2.0	0.82

Despite good CPAP use there is no significant differences in the variables included in table 8.2 between CPAP and placebo.

8.4 Spectral Analysis Results.

Using the ECG and the Finapress data collected, power spectral analysis was performed as previously discussed in chapter 4. At the end of the study all the data were analysed using the software described, and the two data sets are compared using a MANOVA. The results in table 8.3 overleaf are the values computed comparing CPAP therapy and oral placebo.

Table 8.3: Spectral Analysis Results.

	CPAP		Placebo		P-value
	Mean	SEM	Mean	SEM	
Mean PI	986	38	956	34	0.13
Mean SBP	119.7	3.8	123.3	5.4	0.49
Total PI power	7360	1493	6614	1423	0.50
Total SBP power	113.6	23.6	117.9	28.1	0.87
VLF PI power	1918	384	1521	370	0.30
VLF SBP power	62.0	14.4	63.8	20.4	0.92
BRS VLF	6.2	0.7	5.9	0.9	0.63
LF PI power	2198	555	1642	326	0.17
LF SBP power	30.9	8.6	28.9	7.8	0.82
BRS LF	9.0	1.1	9.0	1.1	0.98
HF PI power	1607	456	1720	55	0.77
HF SBP power	5.7	1.0	5.6	1.0	0.96
BRS HF	16.9	3.1	15.2	2.1	0.29
Alpha	12.9	2.0	12.1	1.5	0.40
BRS LF/HF	0.59	<0.01	0.63	<0.01	0.56
LF/HF PI power	2.1	0.5	2.1	0.5	0.94

Legend: *PI - pulse interval;*
SBP - systolic BP;
VLF - very low frequency;
LF - low frequency;
HF - high frequency;
BRS - baroreflex sensitivity.

8.5 Discussion.

This study showed no alteration in baroreceptor function with CPAP compared to placebo. While this may reflect relatively low power in this small component of the overall study, this finding is compatible with the data from Brooks' dog model of sleep apnoea in which there was an effect on 24-hour blood pressure but no change in baroreceptor function.

Conflicting evidence has been produced postulating that patients with OSAHS have high sympathetic activity during wakefulness and during sleep and this has been shown experimentally [376,458]. Cardiovascular stress tests have also reinforced this observation of high sympathetic discharge in the daytime compared to 'normal' controls [507-509]. Sachs et al studied 13 OSAHS patients, 9 narcoleptics with age-matched controls, showing that both conditions are associated with autonomic dysfunction. There was marked inter-individual variations, suggesting a more multi-factorial aetiology [507]. There were differences between the two sleep disorders in the dysfunction's found and the controls were not as closely matched as would be ideal. The main differences were found in heart rate and blood flow in the resting limb on muscle activation, and respiratory sinus arrhythmia, which were diminished compared to healthy controls. These results suggested that there was impairment of the balance between sympathetic and parasympathetically mediated cardiovascular reflexes, possibly at a central level. The patients were not restudied after treatment had been initiated to see if the degree of impairment altered [507].

Cortelli studied 21 normotensive OSAHS patients and 20 age matched controls looking at cardiovascular reflex tests. This study also showed abnormalities in

autonomic function in the OSAHS patients, they did not go on to study a treated group of patients [509]. A further study of autonomic function on OSASHS patients is reported by Veale, who studied 33 patients attending for sleep study [508]. They studied the group night and morning, i.e. before and after their sleep study. In the severe OSAHS patients (n = 12; median AHI 44/hour slept) significantly more of the autonomic tests were abnormal, compared to non OSAHS patients (n = 11). They did not include a control group and did not attempt to match the normals, who were studied. Because the patients were attending for sleep study, it would not be unreasonable to assume that they were symptomatic in some way, therefore are not a good control population.

Khoo et al [315] looked at the alterations in SNS activity in OSAHS compared to matched controls attempting to control for the altered respiratory activity in this patient group, they show a marked increase in sympathetic activity and a reduction in parasympathetic activity. This alteration to the parasympathetic activity may also be one of the factors in the development of cardiac arrhythmias in this patient group. It has previously been shown that CPAP reduced the sympathetic activity in patients with OSAHS [376].

Heart rate variability (HRV) and baroreceptor sensitivity (BRS) are markers of the autonomic control on the heart, HRV reflecting cardiac vagal tone, and BRS reflecting vagal reflexes. BRS assumes a connection between a stimulus and a response, and represents the capacity to reflexively increase vagal activity and sympathetic activity in response to a sudden increase in blood pressure.

There is increasing interest in the role of the ANS in triggering sudden cardiac death following myocardial infarction [510] and it could be related to the rare sudden deaths in

OSAHS, which may be cardiac in origin. Proven alterations in the ANS in this patient group would strengthen this argument.

A difference in BRS may have not been elicited in my study for several reasons, including that:

- The study population is too small, noting that there is no significant difference in BP in this sub group of patients.
- Daytime BRS may be unaffected by the nocturnal swings in BP in the untreated OSAHS patient. The evidence of change in daytime BP in the main study is relatively weak and in addition it is possible to affect BP with out affecting the BRS slope.
- The relatively short duration of the study, however this is less likely as it has been previously shown that here may be a reduction in SNS traffic almost immediately on starting CPAP [440].

The effects of hypoxia on the SNS have also been described [310,511] and it is difficult to explore which of these insults is the dominant problem in this patient group. The DI for this group was certainly at a level that changes in BP would be expected to be seen comparing the data from the chapter 5.

Chapter 9.

Microalbumin as a Marker for Renal Disease in OSAHS Patients.

9.1 Introduction.

It has been recognised in recent times that even slight increases in the urinary albumin excretion can be a valid predictor of premature morbidity and mortality from cardiovascular diseases. In addition increases in albumin excretion provide an early sign of nephropathy in diabetics (both insulin and non insulin dependant) and in the hypertensive population [512-517]. It is a marker used in many diabetic clinics to identify those patients requiring early intervention. I therefore wanted to examine urinary microalbumin in a subgroup of my patients to see if this simple test could perhaps be used as a marker for those patients who might be more at risk of the long-term consequences of OSAHS.

The aim of this study was to measure urinary microalbumin in a sub group of OSAHS patients to determine if it was a reliable marker of long-term health consequences of the disorder. It is a relatively cheap test at approximately £7.00 per sample, simple to perform and if it provides a useful method of predicting those patients who run into trouble with end organ damage it might be worthwhile to add to the battery of investigations done when assessing the OSAHS patient.

9.2 Microalbuminuria.

Proteinuria is a common indicator of renal disease; it can be detected by dipstick testing using an appropriate kit. These dipsticks detect a protein content of >200 μg/min and they react primarily to albumin, and are relatively insensitive to globulin's and Bence-Jones proteins. In the urine, albumin is normally present in concentrations of < 20 μg/min, and the range of 20-200 μg/min is referred to as microalbumin, which is therefore by definition not picked up by dipstick testing. Microalbumin is therefore defined as a urinary albumin excretion rate of 20-200 μg/min. To convert this figure to mg/24 hours it is multiplied by a factor of 1.44. For spot urinary concentrations it is assumed that the average person passes 1.5 litres of urine per day, therefore the mg/24 is divided by 1.5 and is expressed as mg/l. Microalbumin is measured in a spot urine sample by radioimmunoassay. Our local laboratory measures microalbumin, quoting levels of ≥ 10 mg/l as abnormal. Total 24-hour urinary excretion may be measured, and microalbumin is then defined as an excretion rate between 20 and 200 μg/min. Assuming a normal urinary output this corresponds to albumin concentrations of > 15 or 20 mg/l [518].

Normal reference ranges exist for albumin excretion in normal subjects [519]. Several studies have been published both in adults and children. Taking the data from five adult studies [519], 323 individuals were studied and the range of normal (95% of population) albumin excretion was from 1.6 to 3.9 mg/l, in this cohort. This is the standard reference source used [519]. Confounding factors exist; the urinary albumin excretion rate is variable in itself and can be affected by urinary tract infections, cardiac decompensation, hypertension, exercise and poor metabolic control. In this

study group we have excluded cardiac failure, hypertension and diabetes and unfortunately our patient population is not renowned for taking vigorous exercise, so these are already factored out with the recruitment criteria.

9.3 Methods.

Consecutive patients were invited to participate in this study. It was added on to the main BP study at a later stage with the final 21 patients taking part, providing a spot urine samples for analysis.

9.3.1 Samples.

A random urine sample was obtained from patients prior to CPAP commencement. The samples were analysed by the Biochemistry Department in the Royal Infirmary of Edinburgh, which measured the urinary albumin (mg/l) and creatinine (mmol/l) by radioimmunoassay, and used these results to calculate an albumin to creatinine ratio (mg/mmol).

9.4 Results.

9.4.1 Patient Subgroup.

The characteristics of the 21 patients are included in Table 9.1.

9.4.2 Demographics.

Of the 21 patients providing urine samples 19 were male and 2 female. CPAP use in this patient group was 4.0 hours/night (SEM 0.7).

Table 9.1: Demographics of Patients Participating in The Microalbumin Study.

	Mean	SEM
Age (years)	49	2.6
AHI/hour slept	49	8.0
EEG arousals/hour slept	51	6.3
4 % DI/hour slept	20	6.0
BMI kg/m^2	29	0.9
ESS (ex 24)	14	1.2
Partner ESS (ex 24)	15	1.0

9.4.3 Urine Results.

Table 9.2 contains the urinary data from this sub-population. In the majority of patients this was <10 mg/l and therefore insignificant, and hence no ratio could be calculated. However in 35% of patients the results were abnormal.

Table 9.2: Random Urine Results for Study Population.

Patient reference number	Urinary Albumin (mg/l)	Alb/creat ratio (mg/mmol)	Urinary creatinine (mmol/l)
150	<10	*	6.2
151	<10	*	7.1
152	10	<0.1	10.8
153	30	1.4	21.1
154	<10	*	6.2
155	<10	*	14.7
156	11	1.2	9.1
157	16	2.3	6.9
158	<10	*	10.3
159	<10	*	3
160	48	1.9	25
161	<10	*	8.1
162	44	2.8	15.8
163	<10	*	1.5
164	<10	*	6.3
165	12	<0.1	23.4
166	<10	*	15.9
167	<10	*	8.8
168	<10	*	5.2
169	29	<1.0	30.1
170	<10	*	10.7

**denotes unable to calculate ratio*

Normal albumin/creatinine ratio is 0-3.5 mg/mmol from our local biochemistry laboratory.

The mean value of urinary albumin in the eight patients who had abnormal results is 23.6 mg/l, with a range of 10-48 (SEM 4.9).

9.4.4 Relationship Between Urinary Albumin Concentration and OSAHS Measures.

Pearson's bivariate correlation's are used to compare urinary albumin concentration and primary OSAHS outcome variables (Table 9.3). There is no significant correlation between urinary microalbumin and the OSAHS variables listed below however there is a trend to significance with BMI (p=0.06). It is therefore not clear whether it is the OSAHS or the BMI that is the important factor in urinary microalbuminuria.

Table 9.3: Correlational Relationships Between Urinary Albumin and OSAHS Variable.

OSAHS variable	Urinary albumin concentration (mg/l)	p-value
AHI (events hr/slept)	0.24	0.53
EEG arousals (hr/slept)	0.48	0.20
ESS	0.25	0.52
CPAP use	0.30	0.42
BMI	0.65	***0.06***

9.4.5 24-hour Blood Pressure.

The 24-hour BP profiles are available for this subgroup of patients and the results are included in table 9.4 below. This subgroup of the cohort had no significant difference in SBP, DBP, MAP, heart rate or pulse pressure with CPAP. This may just reflect that the sample size is too small, resulting in an underpowered study.

Table 9.4: 24-hour Blood Pressure in This Subgroup.

	CPAP (SEM)	Placebo (SEM)	CPAP v Placebo p-value
SBP (mmHg)	126.9 (2.0)	126.6 (1.9)	0.82
DBP (mmHg)	77.9 (1.2)	78.5 (1.4)	0.59
MAP (mmHg)	94.4 (1.5)	94.0 (1.3)	0.80
Heart rate (bpm)	77.2 (2.3)	77.1 (2.1)	0.78
Pulse pressure	48.9 (1.4)	48.1 (4.5)	0.29

9.5 Discussion.

In this pilot study 35% of the patients had abnormal urinary microalbumin results. It is not clear whether the OSAHS was the cause of the abnormal results or whether they are as a consequence of another problem. With the selection criteria for the study the common problems that would normally lead to microalbuminuria were excluded. Therefore the presence of microalbuminuria may reflect occult disease in this group of patients. There is a trend to significance with correlation with BMI, and perhaps the abnormal results are a reflection of obesity rather than OSAHS.

Although these results are interesting the sample size is small. Further work is needed in this area studying a larger population. Perhaps by going on to perform more complex renal investigations to see if OSAHS alters renal blood flow per se or to see if the consequences of OSAHS are to blame with the nocturnal swings of blood pressure having an adverse effect on the kidney. Furthermore going on to study if there would be any improvement once treatment with CPAP had been established. It has also to be remembered that the urine samples taken are spot samples, and it would be more accurate to perform 24-hour collections to look at protein content and creatinine clearance. However this would be a much more cumbersome study and less attractive to patients to participate, and the object of this study was to see if utilising this simple test was useful in this disorder. The spot urine samples also introduce more variability, with variable urine outputs between patients and therefore the concentration of the urine differs. There is also variability of urinary microalbumin at time of day, with the levels generally being lower during the night. In this study I tried to collect all the samples first thing in the morning. The calculations performed assume an average daily urine volume of 1.5 litres, thereby inducing error. The hope was to see if this simple test was a useful predictor in identifying a possible high-risk population attending the Sleep Clinics. I have raised more questions than answers at present.

Data has been provided in the diabetic, hypertensive and elderly populations trying to predict the usefulness of microalbumin measurements. In the hypertensive population microalbumin has been used as a predictor for cardiovascular mortality [520]. In this large study (n = 439) performed over 6 years, they concluded that microalbuminuria is an independent predictor for cardiovascular mortality in treated

hypertensive men with non-insulin dependant diabetes. However it was macro-albuminuria i.e. proteinuria, that predicted mortality in the non-diabetic group. Further data from the same group with a sample of 333 treated hypertensive men who did not have diabetes; show microalbuminuria to have a low sensitivity as a marker for concomitant cardiovascular disease [521]. It was associated with insulin resistance, which may reflect why our data is trending towards an association with BMI.

There was conflicting data from a large cross-sectional study of 1254 hypertensive patients attending a hypertension clinic, including a variety of other diagnoses, concluding that microalbuminuria was a pressure dependant functional phenomenon in the renal tract, and it was associated with permanent atherosclerotic abnormalities in the whole vascular system [522]. Other studies published have suggested that microalbumin was associated with early cardiovascular morbidity and mortality [513,514,516,523].

Although the evidence to date is contradictory there is no doubt that microalbumin is a useful marker in the diabetic population, possibly in the hypertensive population. However its role in the OSAHS population needs further study.

Chapter 10.

Compliance on Study Treatments.

10.1 Introduction.

CPAP was introduced more than 20 years ago [228] and has remained the standard treatment for OSAHS. Over the years there has been a considerable amount of data discussing the use of CPAP. CPAP has been well validated as a treatment of OSAHS both in terms of improvements in sleepiness [131,524], cognitive function [136,144], driving [525], and health status [155,526]. There has been a variety of study designs over the this time, the most informative studies have taken the design of a randomised controlled trial either using a crossover design or a parallel group, providing the best evidence for the efficacy of this treatment [135,136,140,159,173,177,235,238-240,505,527-529].

10.2 Methods.

The two 'treatment' modalities that were chosen for this study are standard CPAP and an oral capsule, as a placebo. These modalities are discussed below in detail.

10.2.1 Continuous Positive Airway pressure.

CPAP is currently the best-proven treatment for OSAHS as discussed in Chapter 1. For the purpose of this study all patients were issued with Sullivan-V elite CPAP machines (ResMed, Australia). These machines allow calculation of average nightly use using in-built pressure sensitive time clocks, giving the number of hours the

machine is within 2.0 cmH_2O of the prescribed pressure per night. Thus the use time recorded has to genuinely reflect the patient's use and cannot result from the patient leaving the machine switched on in the corner of the room. The machine also contains an automatic stop feature that when the mask is removed the machine shuts down. The elite machines store data for 200 days, which can be downloaded to a PC via an interface, using compliance (SCAN 2.0) software. This allows calculation of an average nightly use of the CPAP units during the study, as well as the night-by-night data. This facility allows compliance to be objectively measured, which is often omitted in earlier studies, which have relied on self-reported compliance which over estimates patients use.

The machines are attached to the patients with a hose and a nasal or full-face mask, a variety of masks are used during this study to facilitate the best fit for the patients to optimise comfort whilst minimising leak. Mask fitting was initially done by specialist nursing staff or technicians during the education session, or by myself. Mask refitting was done if necessary during the study by myself to ensure the best possible mask fit, comfort, and therefore maximise CPAP use.

10.2.2 Placebo.

Lactose capsules were purchased from Nova laboratories Ltd, Leicester. The capsules are plain white and packed in tubs of 28. Patients were told that they were an experimental treatment that might affect the muscle tone in their upper airway and therefore possibly improve their symptoms. Patients were asked to take their

medication before going to bed. Any left over medication was collected at the end of the capsule treatment limb to allow calculation of compliance.

The patients general practitioners were supplied with a sealed envelope containing details of the capsule to be opened in the event of an emergency or if there was a problem and the patient was unable to contact the Sleep Centre for advice. During this study no envelopes required to be opened. The general practitioners were asked to destroy the envelope at the end of the study.

10.3 Results.

10.3.1 CPAP Use.

In this study the mean CPAP use was 3.3 hours per night (SEM 0.3), with a range of 0 to 8.1 hours per night. CPAP use during the two nights that the patients were wearing the ABPM was also analysed, which showed a CPAP use of 3.7 (SEM 0.3) hours per night with a range of 0 to 9.1 hours. Using a paired t-test there is a significant difference in CPAP use in the month compared to the two nights when the ABPM was worn ($p= 0.007$). This presumably reflects the patients being aware that they would be visiting the centre and have their CPAP use examined. Overall CPAP use was lower than I would ideally like. However it is similar to the use previously observed in intention to treat trials, recruiting consecutive patients [135,136,239,242,530].

The patient group reported the common minor side effects of mask discomfort, nasal stuffiness, noise disruption for both the patient and the partner. The majority of these

were dealt with the simple measures of mask refitting, intra nasal steroid, Olbas oil instilled into the filter, humidification and position of the CPAP unit.

The patient group varied from mild to severe disease, both in terms of AHI and symptoms. I went on to look at the more severe cases in terms of AHI and showed the CPAP use increases with increasing AHI, as previously reported. The figures are demonstrated in table 10.1 with the CPAP use increasing to 4.7 hours per night (SEM 0.7) in patients with an AHI ≥ 60 events per hour slept.

Table10.1: CPAP Use in Relation to Increasing AHI.

AHI Hour/slept	Number of patients	CPAP Use Hours/night	SEM	Range
≥ **30**	44	3.5	0.3	0.1-8.1
≥ **40**	28	3.8	0.4	0.1-8.1
≥ **50**	18	4.0	0.5	0.6-8.1
≥ **60**	12	4.7	0.7	0.6-8.1

Another way to look at increasing severity is the desaturation index, however this did not correlate with CPAP use, (r= 0.052, p=0.676). The ESS is not a useful predictor for CPAP use (r=0.163, p=0.185) in this study.

10.3.2 Capsule Use.

Capsule compliance was monitored by collecting any left over medication at the end of the treatment limb. The median number of capsules missed was 0 with a range of 0-10 (Confidence interval 0.5-1.56). This is a very crude method, however there is

no easy way to check compliance with oral medication, if the patient wishes to deceive it would be easy as the capsules could be disposed of rather than returned. However the patients were not informed that any left over medication would be collected at the end of each treatment limb.

10.4 Long Term Follow-up.

Sixty of the sixty-eight patients who completed the study remain on CPAP therapy after a year. Seven have returned their CPAP units, five of these have been referred for MRS devices and one has been lost to follow-up. The patients who continue to use CPAP have a mean compliance of 3.75 hours/night (range 0-9). This is in keeping with previous studies, with the usual spread of CPAP use, or even a little better as the work by McArdle showed 20% of patients give up CPAP use in the long term, in this group so far it is 12% [229]. This patient group received extra support at the start of CPAP therapy, which has been shown to improve compliance [230,231], although their nightly compliance was not as good as I would ideally like, so far the patients are remaining on therapy for longer. It has to be remembered that generally patients who participate in studies are a more compliant population than the population as a whole, which may be reflected in the continued CPAP use.

10.5 Discussion.

An oral placebo was chosen for this study. There is no ideal placebo for CPAP; the options are either 'sham' CPAP or an oral agent. 'Sham CPAP' uses the CPAP unit set at a low pressure, i.e. subtherapeutic. At the inception of this study there were

some concerns that sham CPAP may even make patients worse [531], and because of this I chose an oral placebo.

I was also concerned our patients might be able to distinguish the difference between 'sham CPAP' and therapeutic CPAP. If patients are able to distinguish between the different pressures they would cease to be blinded in a cross over study which is why the Oxford group have performed parallel group studies using sham CPAP [404,537]. A CPAP unit set at minimum pressure might theoretically stabilise the airway sufficiently to treat some episodes of upper airway narrowing, and therefore reduce the effect of a true placebo as it provides partial treatment [103], further biasing results.

The other reason an oral placebo was chosen was that a CPAP machine set at sub-therapeutic pressure might keep the patient awake, thus falsely raising blood pressure and predisposing to finding false benefit from real CPAP. This does not appear to be the case in more severe patients [532] but there is as yet no evidence in milder patients.

I was also concerned that patients would use 'sham CPAP' less than active CPAP as they would not perceive any symptomatic benefit to counterbalance the inconvenience, and thus a true placebo benefit might not be obtained at the end of the study limbs when the key measurements were made. If the patients did not derive benefit from the sub-therapeutic CPAP they may be less compliant with therapeutic treatment, as it has been well documented that the early use of CPAP predicts long-term use [229,533]. If the patient was on the sub-therapeutic limb first they would not necessarily derive any benefit and they would perhaps be less willing to persevere with the treatment limb of the study as my study was of crossover design. The way round this would be to do a parallel group study as done in other centres, but then

you are confronted with matching controls to the study groups, rather than using each patient as their own control.

There are also disadvantages with an oral placebo:-

- There is no matching for the machine, which may have some mystical effect.
- Some patients do not like taking "medicine".
- The patients needed an explanation why they were trying a tablet and we agreed with approval of the ethics committee to tell them that "the medication might improve their upper airway tone thereby reducing the number of apnoeas and therefore reduce their symptoms". This view has been challenged [534] and in turn we have rebutted these claims [201]. These are difficult issues to which there is no clear answer and I can honestly say I have tried an approach I believe is valid and reasonable.

To provide a good evidence base as we are increasingly asked to do, the best evidence comes from the basis of randomised controlled trials (level A evidence-SIGN). This study was formulated with this in mind. There was no long-term intention to deceive the patients, however they had to believe the oral capsule was an active treatment otherwise it would not have been a true placebo. All patients who participated in this study were informed by letter of the contents of the capsule at the time of study completion. At the end of each patient's trial they were told of their own results, and any abnormal BP results were copied to the patients general practitioner.

Overall the size of the placebo effect found in our studies for ESS is similar to that found with sham CPAP suggesting that placebo tablets are as effective placebos as sham CPAP. I believe there is no perfect placebo for CPAP.

The CPAP compliance is lower than ideal as previously stated, this may have been as a result of many factors. This study included a very heterogeneous group of patients with a variety of symptoms and spectrum of AHI's. It was an intention to treat study and consecutive patients are recruited to the study, they were only excluded on the grounds mentioned in Chapter 4, so all suitable patients are approached. It has to be remembered that the Sullivan V elite machines measure time at pressure only, so when the mask is off the face, or there is a large leak this will not appear on the time clock. Also the ramp times do not appear either, as the machine is not at pressure. The majority of patients utilise the 20-minute ramp time. If a patient takes longer to get to sleep, often they tend to restart the ramp time, or if up in the night; on getting back to bed the ramp time can be reset. This results in an underestimate of time wearing the mask, and for example with three 'ramp periods' a further hour would not be recorded.

There has been evidence showing night-to-night variability in OSAHS, which with standard treatment, a single pressure is set which attempts to treat all events. Because of this variability of the disorder CPAP units have been developed to provide a variable pressure, in an attempt that it will make CPAP more comfortable and therefore improve compliance. These units or 'Auto CPAP' vary pressure according to the level of obstruction present, to keep the airway patent.

A recent systematic review of the literature defined three types of placebo, pharmacologic (as in our case), physical (e.g. a manipulation), or psychological (e.g.

a conversation). One hundred and thirty trials were identified, of which the authors looked at 114, excluding 16 on the basis they lacked relevant outcome data. These trails included data from 8525 patients. In conclusion they found no evidence that any placebo had marked clinical effects, they possibly had some benefits in studies with subjective outcomes [535]. It must also be remembered that the research setting itself can change behaviour. There has also been some concern raised about the ethics of using placebos generally. The first placebo-controlled trial was probably performed in 1931 in the treatment of tuberculosis. Since then there has been controversy surrounding their use. One major concern was that patients who received a placebo of any sort is denied the active treatment, this is especially a concern if a trial is of considerable length. There remain two schools of thought one stating that a placebo should only be used if there is no increased risk of death associated with its use, and the other suggests placebo use should be banned if an effective therapy already exists [536].

I felt justified in using an oral placebo in this study for the reasons stated above. The patients were not denied active treatment for any significant length of time, and in excluding hypertensive patients I obviated the need to stop any medication to permit washout, and therefore there was no need to leave hypertensive patients off their anti-hypertensive medication. This latter method has been used in many studies in this area previously however I felt this was not ethical.

Chapter 11.

Future Work.

This study raises more questions than answers. The mechanisms for change in BP need to be teased out further, with further investigation of the sympathetic nervous system, the parasympathetic system and vascular reactivity and remodelling. A better method for measuring BP that does not either affect sleep or cause an arousal from sleep affecting results would provide an ideal tool for further studies. There is a device on trial which could possibly fulfil this role (Innerspace device). This sort of device would be ideal, as it would provide a true reflection of BP profile beat by beat.

It would also be interesting to follow up the patients after they had been on CPAP for a significant time to see if their BP was sustained or indeed whether it fell further. The changes in BP with different treatments for OSAHS, such as the mandibular repositioning splints should be investigated to determine if similar BP changes were seen with these devices.

The microalbumin data is very limited, only a very small number of patients were studied. Further work looking more sophistically at renal function would be informative and to perform a much larger cohort study examining the results, also correlating them with blood analysis of renal function and blood glucose levels.

The changes of daytime BP in OSAHS are starting to be clearer with the evidence available from the dog data [388], data from our study [153] which has been complimented with the data from both the Oxford group [404,537] and the Marburg group (verbal

communication). The canine data provided very convincing results with the BP returning to baseline values when the apnoeic insult was removed, but this was a very acute study in another species. In humans the BP may not change back to 'baseline' as some irreversible damage may be done by the insidious onset of the disease, and often the long time to diagnosis and treatment. Further studies are needed to try and work out what these factors are and see if there are any mechanisms to make them reverse. Perhaps by looking specifically at vessel wall stiffness or examining markers such as endothelin or vasopressin might provide some answers. In addition this pilot data on baroreceptor function and on micro-albuminuria needs extending. There is no doubt that there remain many unanswered questions in the pathophysiology of OSAHS and the scope for further research is huge.

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Appendix 1.

Patient information sheet.

Functional outcomes of sleep questionnaire (FOSQ).

Example of ABPM printout.

Example of steer clear printout of a sleepy patient.

Example of steer clear printout of the same patient after one month of CPAP therapy.

PATIENT INFORMATION SHEET

What the study would involve is:

I am looking at a capsule, which may improve the upper airway tone against the conventional treatment of Continuos Positive Airway Pressure (CPAP for short). I am also looking at changes in blood pressure both in the day and during the night in patients with Sleep Apnoea.

You would get either the capsule first followed by CPAP or vice versa. Each treatment period lasts for 28 days i.e. 56 days in total. I will see you at the start of the study on the night you are due to come up to the Sleep Centre in Ward 48. I will do some tests with you in the evening before bedtime and then the CPAP machine will be set up for you overnight as normal. I will keep in touch by phone on day 5 and 15 of each month and come and visit you at home if necessary. You will then be asked to visit the Sleep Centre in Ward 48 on the evening of day 26 to perform some concentration tests and to allow me to attach a blood pressure monitor, which you will wear for the next 48 hours. I will visit you on day 28 to collect the machine and give you the equipment for the next month. The second month of the trial will run in the same fashion. After the trial period you will receive a CPAP machine to use and be followed up in the clinic as normal.

I will also be asking you to fill out some questionnaires. At each visit to the Sleep Centre I will be asking you to perform concentration tests. I will also measure your weight and waist and neck size at each visit to the Sleep Centre.

This study will involve two extra trips to the Sleep Centre for you, on top of your overnight study to get the CPAP machine set up for you. These extra visits are to allow me to perform the concentration tests and to fit the blood pressure monitors. I will refund travelling expenses for these extra visits.

You are under no obligation to participate in this study and you can withdraw at any time without detriment to your future care.

All data collected will be confidential. Your General Practitioner will be informed of your participation in the study and of any abnormal results.

You can contact me at the Laboratory at any time to discuss this further on 0131 536 4192 or 0131 536 2355.

You can also contact Dr T.Mackay on 0131 536 1000 for unbiased advice on aspects of this study.

Dr J.F. Faccenda

Research Fellow to Prof. N.J. Douglas

Name: **Date:**

FUNCTIONAL OUTCOMES OF THE SLEEP QUESTIONNAIRE (FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. The words do <u>not</u> refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please put a tick (□) in the box for your answer to each question. Select only <u>one</u> answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1 Do you have difficulty concentrating on the things you do because you are sleepy or tired?		□	□	□	□
2 Do you generally have difficulty remembering things, because you are sleepy or tired?		□	□	□	□
3 Do you have difficulty finishing a meal because you become sleepy or tired?		□	□	□	□
4 Do you have difficulty working on a hobby (for example, sewing, collecting, gardening) because you are sleepy or tired?	□	□	□	□	□

Functional Outcomes of Sleep questionnaire (FOSQ)

		(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5	Do you have difficulty doing work around the house (for example, cleaning the house, doing laundry, taking out the rubbish, repair work) because you are sleepy or tired?	☐	☐	☐	☐	☐
6	Do you have difficulty operating a motor vehicle for <u>short</u> distances (less than 100 miles) because your sleepy or tired?	☐	☐	☐	☐	☐
7	Do you have difficulty operating a motor vehicle for <u>long</u> distances (greater than 100 miles) because your sleepy or tired?	☐	☐	☐	☐	☐
8	Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?	☐	☐	☐	☐	☐
9	Do you have difficulty taking care of financial affairs and doing paperwork (for example, writing cheques, paying bills, keeping financial records, filling out tax forms, etc) because you are sleepy or tired?	☐	☐	☐	☐	☐
10	Do you have difficulty performing paid or volunteer work because you are sleepy or tired?	☐	☐	☐	☐	☐
11	Do you have difficulty maintaining a telephone conversation because you become sleepy or tired?	☐	☐	☐	☐	☐

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
12 Do you have difficulty visiting with your family or friends in <u>your</u> home because you become sleepy or tired?	☐	☐	☐	☐	☐
13 Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	☐	☐	☐	☐	☐
14 Do you have difficulty doing things for your family or friends because you are too sleepy or tired?	☐	☐	☐	☐	☐

	(4) No	(3) Yes, a little	(4) Yes, moderately	(5) Yes, extremely
15 Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	☐	☐	☐	☐

In what way has your relationship been affected?

_____

_____

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
16 Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	☐	☐	☐	☐	☐
17 Do you have difficulty watching a film or videotape because you become sleepy or tired?	☐	☐	☐	☐	☐

Functional Outcomes of Sleep Questionnaire

		(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
18	Do you have difficulty enjoying the theatre or a lecture because you become sleepy or tired?	☐	☐	☐	☐	☐
19	Do you have difficulty enjoying a concert because you become sleepy or tired?	☐	☐	☐	☐	☐
20	Do you have difficulty watching TV because you are sleepy or tired?	☐	☐	☐	☐	☐
21	Do you have difficulty participating in religious services, meetings or a group or a club because you are sleepy or tired?	☐	☐	☐	☐	☐
22	Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?		☐	☐	☐	☐
23	Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?		☐	☐	☐	☐
24	Do you have difficulty being as active is you want to be in the afternoon because you are sleepy or tired?		☐	☐	☐	☐
25	Do you have difficulty keeping pace with others your own age because you are sleepy or tired?		☐	☐	☐	☐

Functional Outcomes of Sleep Questionnaire (FOSQ)

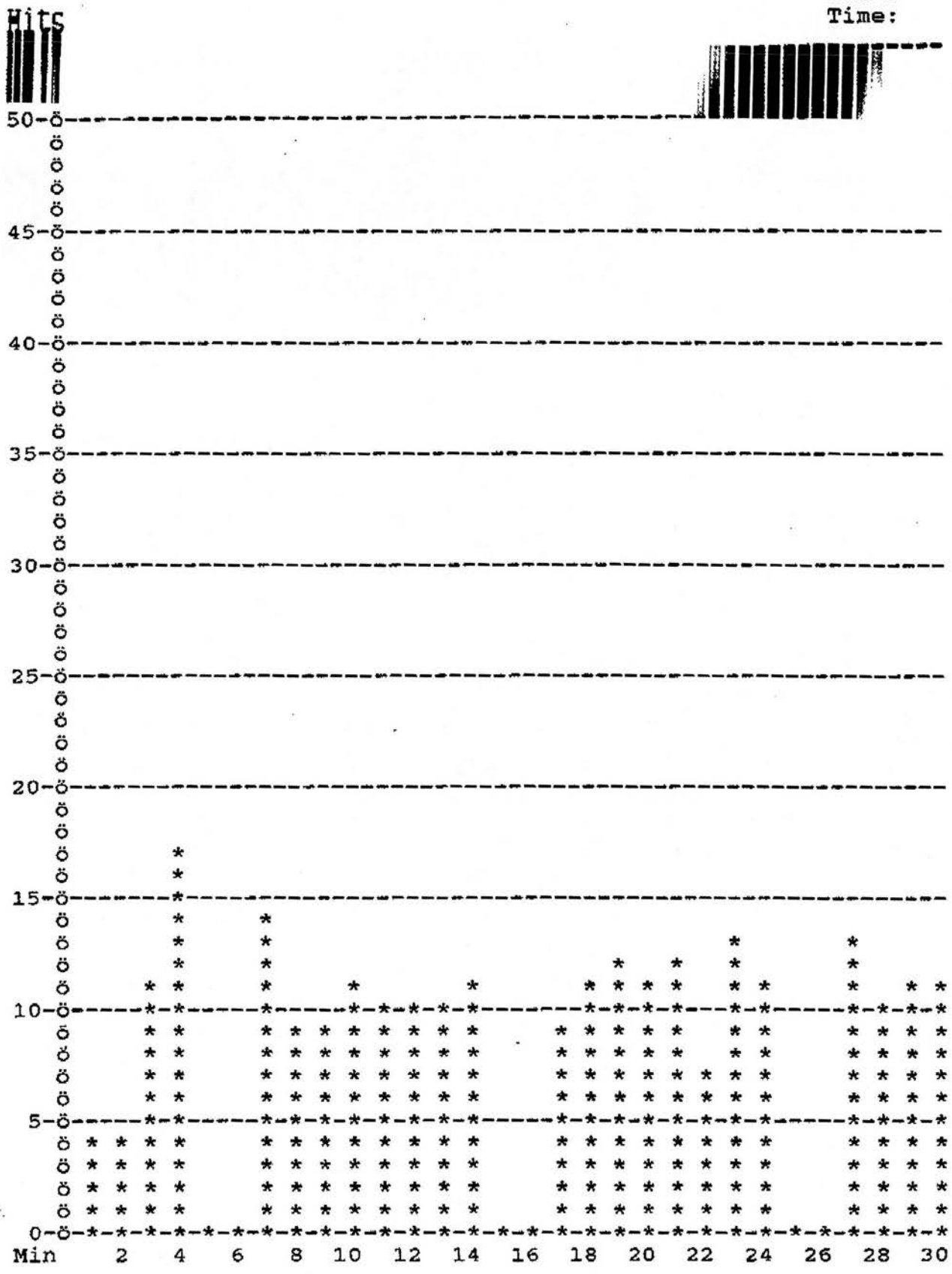
	(1) Very low	(2) Low	(3) Medium	(4) High
26 How would you rate your general level of activity?	☐	☐	☐	☐

Example of Steer Clear Printout in a Sleepy Patient.

HITS BY MINUTE

Name: ci

Study Numb
Date:
Time:

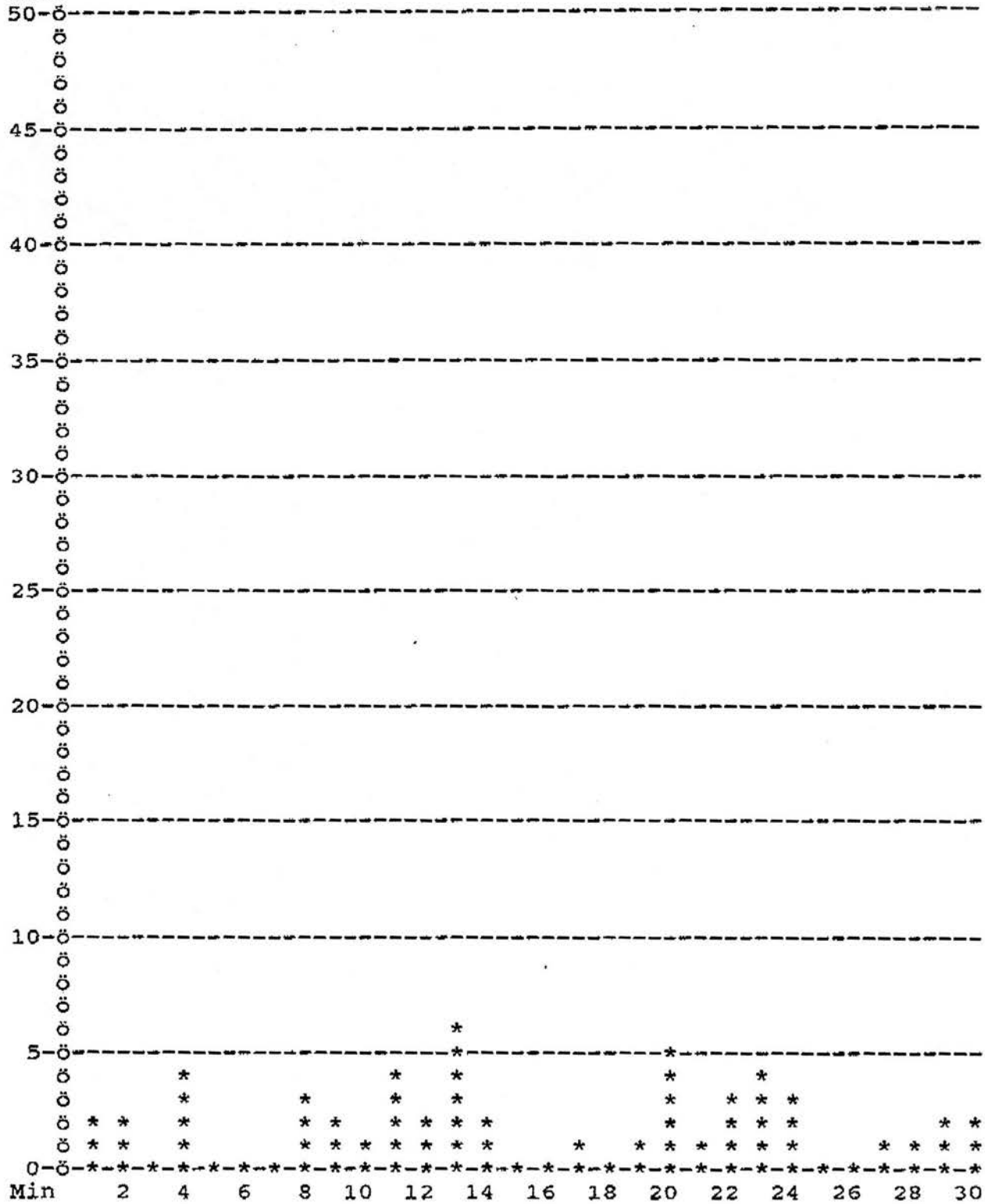


Example of Steer Clear Printout in The Same Patient After One Month of CPAP Therapy.

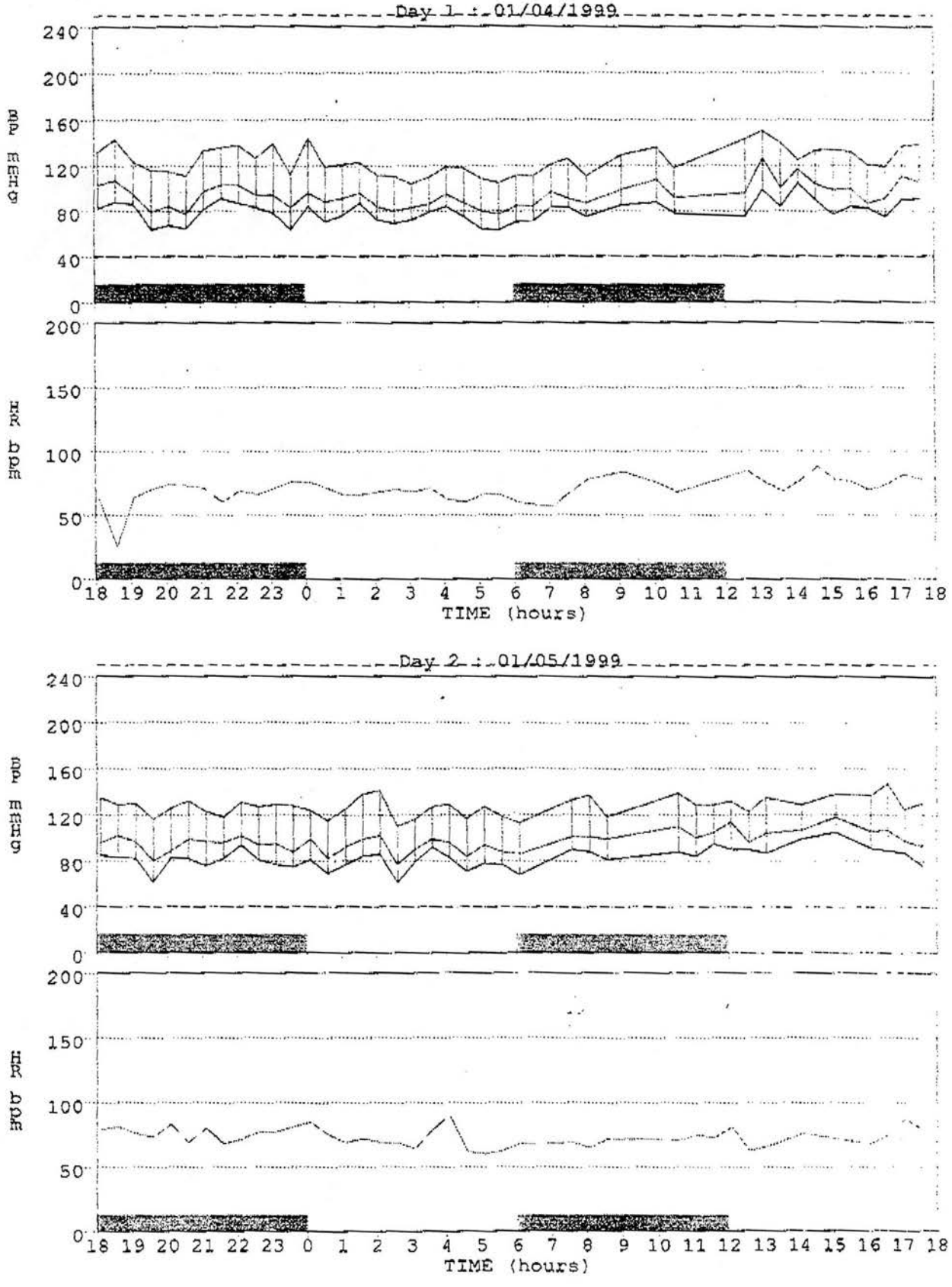
HITS BY MINUTE

Name: ci

Study Numb
Date:
Time:



Sample Graphs From the ABPM Printout.


Day 1 : 01/04/1999
240
200
160
120
80
40
0
BP mmHg
200
150
100
50
0
HR bpm
18 19 20 21 22 23 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
TIME (hours)
Day 2 : 01/05/1999
240
200
160
120
80
40
0
BP mmHg
200
150
100
50
0
HR bpm
18 19 20 21 22 23 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
TIME (hours)

Appendix 2.

Articles, abstracts and presentations resulting from this research.

Original Articles:

Faccenda JF, Mackay TW, Boon NA, Douglas NJ.
Randomized placebo controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea/hypopnea syndrome.
AJRCCM 2001;163(2):344-8.

Douglas NJ, Engleman HM, Faccenda JF, McArdle N.
The science of designing ethical CPAP trials.
AJRCCM 2002;165:132-4.

Abstracts and Presentations:

Faccenda JF, Boon NA, Mackay TW, Douglas NJ.
Randomised trial of CPAP on blood pressure in SAHS.
Am J Respir Crit Care Med 1999;159(3):A527
Presented at mini-symposium and displayed as assembly highlight poster.

Faccenda JF, Boon NA, Mackay TW, Douglas NJ.
Randomised controlled trial of CPAP on blood pressure in SAHS.
Proceedings of the Scottish Thoracic Society, Stirling, November 1999.

Faccenda JF, Boon NA, Mackay TW, Douglas NJ.
Randomised controlled trial of CPAP on blood pressure in the sleep apnoea/hypopnoea syndrome (SAHS).

Proceedings of the World Congress on Sleep Apnoea, Sydney, March 2000.

Faccenda JF, Boon NA, Mackay TW, Douglas NJ.
Quality of life on and off CPAP in patients with sleep apnoea/hypopnoea syndrome.
Am J Respir Crit Care Med 2000;161(3):A213.

Faccenda JF, Boon NA, Mackay TW, Douglas NJ.
CPAP Effects on blood pressure in the sleep apnoea/hypopnoea syndrome (SAHS) during a randomised controlled trial.
Am J Respir Crit Care Med 2000;161(3):A714.

Faccenda JF, Boon NA, Mackay TW, Douglas NJ.
Microalbumin as a marker for end organ damage in SAHS.
Am J Respir Crit Care Med 2001;163(5):A34.

Faccenda JF, Boon NA, Wraith PK, Labinjoh C, Maxwell S, Webb D, Mackay TW, Douglas NJ.
Randomised trial of CPAP on baroreceptor function in SAHS.
Am J Respir Crit Care Med 2001;163(5):A390.

Randomized Placebo-controlled Trial of Continuous Positive Airway Pressure on Blood Pressure in the Sleep Apnea–Hypopnea Syndrome

JACQUELINE F. FACCENDA, THOMAS W. MACKAY, NICHOLAS A. BOON, and NEIL J. DOUGLAS

Respiratory Medicine Unit and Cardiovascular Unit, University of Edinburgh, Royal Infirmary, Edinburgh, Scotland, United Kingdom

Arterial blood pressure rises at apnea termination, and there is increasing evidence that the sleep apnea–hypopnea syndrome (SAHS) is associated with daytime hypertension but no randomized controlled trial evidence of whether SAHS treatment reduces blood pressure exists. We, therefore, conducted a randomized placebo-controlled cross-over study of the effects of 4 wk of continuous positive airway pressure (CPAP) or oral placebo on 24-h blood pressure in 68 patients (55 males, 13 females; median apnea–hypopnea index [AHI], 35) not receiving hypotensive medication. Ambulatory blood pressure was recorded for the last 48 h of each treatment. Epworth Sleepiness Score (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) were also recorded. All patients were normotensive. There was a small decrease in 24-h diastolic blood pressure (placebo, 79.2 [SE 0.9] mm Hg; CPAP, 77.8 [SE 1.0] mm Hg; $p = 0.04$) with the greatest fall occurring between 2:00 A.M. and 9:59 A.M. The observed decrease in 24-h diastolic blood pressure was greater in two *a priori* groups, CPAP use ≥ 3.5 h per night (81.5 [SE 1.2] mm Hg; 79.6 [SE 1.2] mm Hg; $p = 0.03$) and those with more than twenty 4% desaturations per hour (82.4 [SE 2.1] mm Hg; 77.4 [SE 2.1] mm Hg; $p = 0.002$). Systolic pressure also fell in the latter group (133.1 [SE 2.8] mm Hg; 129.1 [SE 2.1] mm Hg; $p = 0.009$). Desaturation frequency was the best predictor of diastolic blood pressure fall with CPAP ($r = 0.38$; $p = 0.002$). Both ESS and FOSQ domains improved. Thus, CPAP can reduce blood pressure in patients with SAHS, particularly in those with nocturnal oxygen desaturation, but the decrease is small.

The sleep apnea–hypopnea syndrome (SAHS) occurs in 1–4% of the middle-aged population (1), causing sleepiness, daytime cognitive deficits, impaired mood, and road traffic accidents (2). Randomized placebo-controlled trials have shown that continuous positive airway pressure (CPAP) therapy significantly improves symptoms, sleepiness (3, 4), cognitive function, mood, and quality of life (5) while controlled trials suggest that CPAP significantly improves driving simulator performance (6).

Considerable uncertainty, however, remains about the effects of the sleep apnea–hypopnea syndrome on the cardiovascular system (7, 8). Apneas and hypopneas are immediately followed by acute rises in blood pressure coincident with the arousal from sleep (9). It is not clear, however, whether this episodic nocturnal hypertension results in sustained daytime hypertension or increased cardiovascular risk. About 50% of patients with the sleep apnea–hypopnea syndrome have daytime hypertension (9, 10) but many have other risk factors for hypertension, including obesity and alcohol consumption. Epidemiological studies, which have tried to factor out these confounders, have concluded that there is (11–14) or is not (15, 16) an independent association between sleep apnea and daytime hypertension. Intervention studies have shown that CPAP can normalize nocturnal blood pressure in patients with the sleep apnea–hypopnea syndrome (17), but the effect of CPAP on daytime blood pressure is unclear. Previous studies of the effects of CPAP on daytime blood pressure have been difficult to interpret because of the difficulty of matching controls (18–21) or, in the one case in which a randomized placebo-controlled design was used, were inadequately powered (22) with only 13 patients studied and no clear conclusion.

Studies of animal models have strongly suggested that sleep apnea may cause sustained hypertension (23, 24). They suggest that while arousal from sleep may cause transient nocturnal hypertension, sustained daytime hypertension occurs only if there is coexisting intermittent nocturnal hypoxemia and not if there is merely sleep fragmentation alone (24, 25).

We have, therefore, carried out a randomized placebo-controlled trial of CPAP therapy on 24-h blood pressure in patients with the sleep apnea–hypopnea syndrome. At the same time we have also examined the effects of CPAP on subjective sleepiness and quality of life.

METHODS

Patients

Consecutive patients referred to the sleep center were considered for inclusion, provided they had at least two major symptoms of SAHS and an apnea–hypopnea index (AHI) ≥ 15 on polysomnography using our previously described techniques (26) recorded on a computerized system (*S* system; Compumedics, Melbourne, Australia). Hypopnea was defined as a ≥ 50% reduction in thoracoabdominal movement sum signal (27). Exclusion criteria included problems with sleepiness when driving, living more than 50 miles from the center, shift work, diabetes, or the taking of medication that would alter blood pressure. One hundred and seven patients were approached and 78 agreed to participate in the study, the remainder declining because of work or family commitments. None of these patients had taken part in any of our previous studies (Figure 1).

Weight and height were measured to allow calculation of body mass index (kg/m^2). The Epworth Sleepiness Scale (ESS; 28) and the Sleep-specific Quality of Life Scale—Functional Outcomes of Sleep Questionnaire (FOSQ; 29) were completed at the start of the study to allow familiarization, and at the end of each treatment limb.

ESS: Subjects score themselves, on a scale of 0–3, on how easily they would fall asleep in eight different situations, giving an overall score between 0 and 24; the higher the score the sleepier the individual.

FOSQ: The FOSQ is a sleep-specific questionnaire developed to reflect the impact of sleep disorders and excessive sleepiness on activities of daily living. It focuses on five different domains: General Productivity, Social Outcomes, Activity Level, Vigilance, and Sexual Relationships and Intimacy. The optional questions on intimacy and sexual relationships were excluded in this study. The questionnaire comprises 26 questions set at a 10-yr-old reading level, which takes approximately 15 min to complete. Each question has a four-point scale with an appropriate column to be checked. The results are processed to give a mean-weighted item score for each of the four sub-

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Correspondence and requests for reprints should be addressed to J. F. Faccenda, MBChB, Respiratory Medicine Unit, Department of Medicine, Royal Infirmary, Lauriston Place, Edinburgh, EH3 9YW Scotland, UK. E-mail: jff@srv1.med.ed.ac.uk

This article has an online data supplement, which is accessible from the issue's table of contents online at www.atsjournals.org

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Internet address: www.atsjournals.org

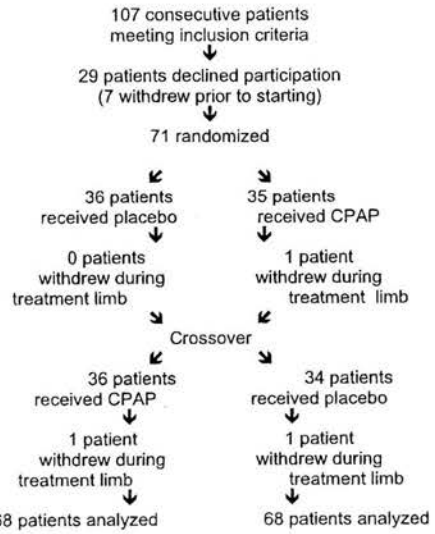

Figure 1. Trial profile.

groups (ex4), which when added together produce a global score. The lower the score the more dysfunctional the individual secondary to sleepiness.

Ambulatory Blood Pressure Monitoring

Patients were fitted with a lightweight microprocessor to collect the BP data via an arm cuff (Ultralite ABPM; SpaceLabs Medical, Redmond, WA) at the end of each treatment limb. The ambulatory blood pressure monitoring (ABPM) module is a small unit weighing 347 g, which is carried on a belt or shoulder strap, connecting to the arm cuff via a rubber hose. A cuff of appropriate size was fitted to the nondominant upper arm, with instructions provided on how to readjust, if necessary. Subjects were asked to continue their normal daily activities, recording these in a diary. The monitor was worn during the whole 48 h, removing it only for bathing. The monitor recorded systolic blood pressure (Psyst), diastolic blood pressure (Pdias), and mean arterial pressure ($\overline{Pa}$).

Protocol

All patients underwent a full-night CPAP titration study using an automated pressure setting device (Auto Set; ResMed, Sydney, Australia). The following morning the patient was randomized, using a balanced block design, to receive either CPAP or an oral capsule for the first limb, and crossed over after 1 mo to the alternative treatment for the second limb. The capsule was a placebo, which patients were told, with the permission of the local ethics committee, might improve the tone in the upper airway muscles. The CPAP units used for home therapy were Sullivan V Elites (ResMed), which were downloaded at the end of the treatment period to obtain a real-time record of the time when the patient was using the device at the appropriate pressure (time at pressure).

Forty-eight hours before the end of each limb, the patients were fitted with the ABPM module. The monitors were fitted in the early evening to all patients, and programmed to record every 30 min for 48 h. Patients were asked to abstain from caffeine-containing products during this time. Data gathered before 6:00 P.M. on the second evening were discarded to allow for acclimatization. The analysis was performed with the second 24 h of data (6:00 P.M. to 6:00 P.M.). All data were manually checked for artifact by an observer who was blinded to the treatment status of the patient.

All patients gave written informed consent to participation in the study, which was approved by the Lothian Ethics of Medical Research Committee.

Data Analysis

The ESS, FOSQ, and blood pressure data (grouped into 4-h means) were analyzed by repeated measures analysis of variance, using the general linear model (SPSS for Windows, version 9, 1998; SPSS, Chicago, IL). When this showed significant difference, MANOVA was used to identify time points when blood pressure altered with CPAP use. Data were analyzed on an intention to treat basis, including all data obtained even if patients were known not to be complying with CPAP therapy. A subanalysis was also performed, using an *a priori* agreed cut point of 3.5 h per night for reasonable CPAP compliance (3). Because of the animal data indicating the importance of intermittent hypoxemia in the pathogenesis of hypertension in sleep apnea (23, 24), we also used an *a priori* cut point of twenty 4% desaturations per hour to indicate those patients with significant nocturnal hypoxemia. Pearson correlation analysis was performed on data that had been shown to be normally distributed.

RESULTS

Of the 78 patients (65 males, 13 females) who agreed to participate, 7 withdrew prior to randomization for personal reasons and 71 started the study. Of the 71, 3 withdrew during the study (1 in the placebo limb and 2 in the CPAP limb). Sixty-eight (55 males, 13 females) completed the trial (Table 1) and their data are reported. Mean CPAP time at pressure in the 4 wk of the study was 3.3 h per night (range, 0 to 8.1 h per night). Capsule counting showed the patients missed a median of 0 tablets (95th percentile, 1.4 tablets) over the month on placebo. There was no significant change in weight between the two limbs ($p > 0.8$). There was no evidence of either order or carryover effects ($p > 0.3$).

Over the 24-h period, on an intention to treat analysis, there was no significant change in systolic pressure but a significant 1.5-mm Hg reduction in diastolic blood pressure on CPAP therapy ($p = 0.04$; Table 2). Analysis of the 4-h time blocks showed that diastolic blood pressure was significantly lower in the 2:00 A.M. to 5:59 A.M. ($p = 0.03$) and 6:00 A.M. to 9:59 A.M. ($p = 0.02$) blocks; there were no other significant changes ($p > 0.1$). These data are available in the online data supplement to this article at www.atsjournals.org. There were no significant changes in either heart rate (placebo, 77 [SE

TABLE 1

DEMOGRAPHICS OF 68 PATIENTS STUDIED

	Median	Range
Age, yr	50	29–72
AHI/h slept	35	15–129
4% Desaturation index/h slept	7	0–128
EEG arousals/h slept	42	12–129
BMI, kg/m^2	30	21–53
Neck, cm	40	33–55
Waist, cm	104	81–145
Hips, cm	108	93–160
ESS, ex24	15	6–24
Partner ESS	14	4–24

Definition of abbreviations: AHI = apneas + hypopneas per hour slept; BMI = body mass index (kg/m^2); EEG = electroencephalogram; ESS = Epworth Sleepiness Score.

TABLE 2

MEAN BLOOD PRESSURE OVER 24 h IN ALL 68 PATIENTS

	CPAP		Placebo		Differences		
	Mean	SEM	Mean	SEM	Mean	95% CI	p Value
Psyst, mm Hg	126.9	1.3	128.2	1.2	−1.3	−3.3 to 0.7	0.19
Pdias, mm Hg	77.8	1.0	79.2	0.9	−1.5	−3.0 to −0.1	0.04
$\overline{Pa}$, mm Hg	94.4	1.0	95.5	0.9	−1.0	−2.6 to 0.6	0.20

Definition of abbreviations: CI = confidence interval; $\overline{Pa}$ = mean arterial pressure; Pdias = diastolic blood pressure; Psyst = systolic blood pressure; SEM = standard error of the mean.

TABLE 3

MEAN BLOOD PRESSURE IN PATIENTS USING CPAP ≥ 3.5 h PER NIGHT*

	CPAP		Placebo		Differences		
	Mean	SEM	Mean	SEM	Mean	95% CI	p Value
Psyst, mm Hg	129.9	2.1	131.0	1.8	−1.1	−3.6 to 1.4	0.41
Pdias, mm Hg	79.6	1.2	81.5	1.2	−1.9	−3.7 to −0.1	0.03
$\overline{Pa}$, mm Hg	96.1	1.4	97.7	1.2	−1.0	−3.1 to 1.0	0.30

Definition of abbreviations: CI = confidence interval; $\overline{Pa}$ = mean arterial pressure; Pdias = diastolic blood pressure; Psyst = systolic blood pressure; SEM = standard error of the mean.

* n = 32.

1.1], CPAP 76 [SE 1.2]; p = 0.4) or pulse pressure (p = 0.8) with CPAP.

Thirty-two patients used their CPAP machines for more than the *a priori* cut point of 3.5 h per night on average and showed a mean decrease in 24-h diastolic blood pressure (Table 3). There was no significant change in 24-h systolic blood pressure in this group. In the 14 patients with 4% desaturation frequencies above 20 per hour on the baseline sleep studies, CPAP therapy produced highly significant falls in 24-h systolic, diastolic, and mean arterial pressures (Table 4).

Using intention to treat data for all 68 patients, the decrease in 24-h diastolic blood pressure between placebo and CPAP was significantly correlated with the frequency of 4% desaturations in the baseline sleep study (r = 0.35; p = 0.002) and with AHI (r = 0.23; p = 0.032). Multiple regression analysis showed that desaturation frequency was the only independent predictor of drop in diastolic blood pressure with CPAP (r = 0.38; p = 0.02).

There was a significant drop in ESS with treatment (Table 5; p < 0.001). The FOSQ data (Table 5) show that three of the four different domains improved significantly with CPAP, as did the overall total.

DISCUSSION

This study shows that CPAP results in a significant fall in 24-h diastolic blood pressure, but when analyzed in all patients on an intention to treat basis, the fall in diastolic pressure is only 1.5 mm Hg. However, the falls in blood pressure were greater in those patients with intermittent nocturnal hypoxemia in whom systolic pressure over 24 h dropped by 4.0 mm Hg and diastolic pressure by 5.0 mm Hg.

Potential problems with this study include the type of placebo used, the lack of a washout period, dropouts, the 1-mo treatment duration, the large number of potential comparisons, and the fact that the patients were normotensive. Normotension was not an entry criterion, but it was required that no patients be receiving hypotensive therapy, and none proved to be hypertensive on entry. We excluded patients taking hypotensive drugs to avoid any confounding effects of hypotensive medication, and did not feel ethically justified to stop hypotensive therapy for the duration of a study in known hypertensives. CPAP therapy is relatively obtrusive and could conceivably have an effect merely due to "machine mystique," which was not found in our tablet placebo. One study has used a CPAP set at a subtherapeutic pressure to investigate daytime function in SAHS (4). Interestingly, the magnitude of the placebo effect with sham CPAP on symptoms in that study was similar to that found by our group with placebo tablets (ESS, Jenkinson and coworkers [4] baseline 15, sham CPAP 13; Engleman and coworkers [5] baseline 13, placebo tablet 11), suggesting that there is no specific "machine mystique" effect of a sham CPAP placebo that our tablet lacks. Furthermore, we used a tablet that was actively "sold" to our patients as an agent that might be effective, with ethics committee agreement, on the basis of the following points.

1. A CPAP machine set at subtherapeutic pressure might keep the patient awake, thus, falsely raising blood pressure and predisposing to finding benefit from real CPAP.
2. We were concerned that patients would use sham CPAP less than active CPAP, as they would not perceive any symptomatic benefit to counterbalance the inconvenience, and thus a true placebo benefit might not be obtained at the end of the study limbs when the key measurements were made.
3. At the time the study was designed, there were reports that subtherapeutic CPAP might cause dangerous hypoxemia (30).
4. A CPAP unit set at minimum pressure might stabilize the airway sufficiently to treat some episodes of upper airway narrowing.
5. Sham CPAP has also to be "sold" to patients as potentially active therapy.

Although we did not include a formal washout period, no measurements were made until 26 d after cross-over. Thus, it is unlikely there would be any carryover effects, especially as in the dog model of sleep apnea, blood pressure normalizes within 1–3 wk of apnea termination (24). Further, any carryover effect would bias against the positive findings in our study. We believe the dropout rate of 3 of the 71 patients randomized, while undesirable, was acceptable and will not have influenced the blood pressure results reported. Patients used CPAP for 4 wk and thus the data from this study cannot be extrapolated to long-term treatment. However, early CPAP use predicts later CPAP use and 95% of those patients using CPAP for more than 4 h at 1–3 mo after CPAP initiation are still using CPAP 7 yr later (31). This suggests that at least in our good user group, sustained treatment is likely.

TABLE 4

MEAN BLOOD PRESSURE IN PATIENTS WITH MORE THAN TWENTY 4% DESATURATIONS PER HOUR*

	CPAP		Placebo		Differences		
	Mean	SEM	Mean	SEM	Mean	95% CI	p Value
Psyst, mm Hg	129.1	2.1	133.1	2.8	−4.0	−7.0 to −4.0	0.009
Pdias, mm Hg	77.4	2.1	82.4	2.1	−5.0	−7.3 to −2.4	0.002
$\overline{Pa}$, mm Hg	95.2	1.8	98.6	1.9	−3.4	−6.3 to −0.6	0.012

Definition of abbreviations: CI = confidence interval; $\overline{Pa}$ = mean arterial pressure; Pdias = diastolic blood pressure; Psyst = systolic blood pressure; SEM = standard error of the mean.

* n = 14.

TABLE 5

EFFECTS OF CPAP

FOSQ Domain (ex4)	CPAP (mean SEM)	Placebo	p Value
General Productivity	3.2 (0.2)	3.1 (0.2)	0.070
Social Outcomes	3.3 (0.1)	3.0 (0.2)	0.010
Activity Level	3.0 (0.1)	2.7 (0.2)	0.004
Vigilance	2.9 (0.1)	2.7 (0.2)	0.029
Total (ex16)	12.4 (0.5)	11.6 (0.7)	0.010
ESS (ex24)	10.1 (0.7)	12.5 (0.8)	0.001

Definition of abbreviations: ESS = Epworth sleepiness scale; FOSQ = functional outcomes of sleep questionnaire; SEM = standard error of the mean.

The study generated a large amount of data, with 13,056 blood pressure recordings (68 × 2 limbs × 48 times [systolic + diastolic]) and thus has potential for finding significant differences due to multiple comparisons. We have adopted a conservative statistical approach, using only intention to treat or two *a priori* subgroup analysis along with conservative data analysis. Furthermore, the data are internally consistent, showing significant changes in the whole population that are larger in the subgroups, in whom greater benefit was predicted. Thus, we believe the number of data points is a strength of our study.

We excluded patients receiving treatment for hypertension, lest this interfere with the effects of CPAP on blood pressure. We did not think it was ethical to withdraw antihypertensive therapy from treated patients for a placebo-controlled trial of an unproven therapy for hypertension. Data from hypertensive populations do not show any "threshold" diastolic pressure below which decreases in pressure were not associated with decreases in stroke and myocardial risk (32). Thus, we believe including normotensive patients was valid.

The mechanism of the blood pressure increases in SAHS is not well understood; however, it has been postulated that the sympathetic nervous system plays an integral part. Previous studies have shown an increase in sympathetic nerve traffic in SAHS which is reduced with treatment acutely (33); this is borne out also in long-term use (34). The latter study did not show a significant reduction in blood pressure or heart rate at 6 mo; however, their patient group included only 11 patients. A further study looked at the acute effects of CPAP on blood pressure in two groups: one group was treated with CPAP and the other group had "sham" CPAP as a placebo. The two groups showed significant reductions in blood pressure, and the authors suggested that the placebo effect was strong; however, recordings were taken after only 1 wk of therapy (35).

This study is the first randomized controlled trial to show that CPAP can reduce blood pressure in SAHS compared with placebo. The previous trials of the effect of CPAP on blood pressure have not only produced conflicting results (16–21, 35), but most have not been randomized (18–21, 36) and variably controlled (18, 35). The only exception was our previous but underpowered study (22).

Our current study found a fall in diastolic blood pressure with CPAP over the time periods 2:00 to 9.59 A.M. Patients were asleep for much of this time and this fall in blood pressure on CPAP during sleep is compatible with acute studies showing that CPAP abolishes nocturnal blood pressure rises by preventing apneas (18–22, 33, 35–38). Our patients' median reported waking time was 7:00 A.M. (95% CI 6:45 to 7:30 A.M.). Thus, significant decreases in diastolic pressure were found at times encompassing both sleep and the first few hours of wakefulness. However, it must be stressed that the 4-hourly analysis did not find any significant decrease in blood pressure with CPAP during most of the waking day.

What is the clinical significance of the changes in blood pressure found in this study? Investigations using conventional antihypertensive agents in non-SAHS populations indicate that a 5-mm Hg decrease in diastolic blood pressure is associated with a 42% decrease in stroke and a 14% decrease in coronary heart disease within a 5-yr period (39). A similar decrease in diastolic blood pressure results in a 31% decrease in stroke and 21% decrease in coronary heart disease, a mean of 10 yr after starting therapy (32). Our hypoxemic patients had a 5-mm Hg decrease in diastolic pressure and thus CPAP therapy in SAHS patients with nocturnal hypoxemia would seem justified on the grounds of pressure reduction alone. Whether the reduction of 1.5 mm Hg in diastolic blood pressure seen in the overall patient group is clinically useful is difficult to determine and might need further evaluation with longer term trials. These could possibly be done in asymptomatic patients, as there is overwhelming evidence of the efficacy of CPAP on symptoms and daytime function (3–5) and long-term placebo-controlled studies of symptomatic patients would not be ethical. However, in clinical practice, the assessment of the value of CPAP therapy in individual patients must include consideration of the symptomatic, cognitive, mood, quality of life (3) and driving (2) benefits as well as any possible hypotensive effect.

This study also suggests that SAHS results in increased 24-h blood pressure profiles, thus confirming the animal studies (23, 24) and some (11–14), but not all (15, 16), of the epidemiological studies. This intervention study has the advantage over epidemiological studies of not having confounders to make interpretation of causality difficult. The study is also compatible with the observation in animal models that nocturnal hypoxemia predisposes to higher blood pressures and probably ultimately hypertension (23, 24).

The significant improvements in ESS seen with CPAP confirm previous work (26). The FOSQ data extend the previous observations (5, 40) of improved quality of life with CPAP as judged by the general quality-of-life questionnaire, the medical outcomes short form 36 (SF-36). This is the first randomized controlled trial to report improvements in sleep-specific quality of life measures with CPAP. These improvements with CPAP confirm the efficacy of CPAP both in this study and in general CPAP use.

Overall, the use of CPAP in this study, while disappointing, was similar to that in our previous studies (3, 5, 22), in which use has been prospectively documented in all patients presenting with a wide range of SAHS severity. CPAP was used as the best of the currently available patient acceptable interventions at abolishing nocturnal events. Although we did not perform further sleep studies during the treatment limbs in these patients, all patients had had CPAP titration studies in our center after study enrolment, which showed a reduction in their apneas and hypopneas to a mean of 6 (SE 1) per hour slept. All studies of CPAP were carried out at that pressure and were completed within 3 mo of the titration study.

The results from this study show that 24-h blood pressure can be lowered by treatment. However, it is hoped that future developments will make treatment of SAHS better used and, thus, perhaps increase the blood pressure reduction obtained.

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Correspondence

INFLAMMATORY MARKERS IN BACTERIAL EXACERBATIONS OF COPD

To the Editor:

Aaron and colleagues (1) recently showed convincingly that inflammatory markers in the sputum of adults with COPD are elevated during exacerbation compared with clinically stable periods. However, their data do not support their conclusion that the inflammatory response observed during exacerbation "appears to occur independently of a demonstrable viral or bacterial infection." In their study, viral infection was established in just two exacerbations and bacteria in a single sputum sample at the time of exacerbation. Based on these numbers, one cannot draw meaningful conclusions regarding the role of viral or bacterial infection in the elevated inflammatory markers seen during exacerbations.

The definition of an acute exacerbation due to bacteria as "demonstration of a new pathogenic organism cultured from sputum on the day of exacerbation, but not cultured at baseline" is problematic. Adults with COPD are colonized by potential pulmonary bacterial pathogens during clinically stable periods. Such a definition does not account for this observation, nor does the definition take into account the dynamic turnover of bacterial strains observed in COPD (2). It would be important to know the results of sputum cultures in the patients studied. The single patient whom the authors concluded experienced a bacterial exacerbation had *Klebsiella pneumoniae* in the sputum, an organism that many authors would question being a cause of exacerbation. Finally, the observation that only 14 exacerbations occurred in 50 patients over a 9 to 15 month period, differs substantially from other prospective studies that show a rate of 1 to 1.5 exacerbations per patient annually (3). Do the authors have an explanation for this difference?

A recent study of 81 exacerbations of COPD showed that inflammatory markers were significantly increased in sputum samples that contained *Haemophilus influenzae* and *Moraxella catarrhalis* compared with sputum samples that contained no bacterial pathogens at the time of exacerbation (4). Another study involving 121 patients with COPD showed that bacterial pathogens in sputum are associated with neutrophil influx (5). In addition, Hill and colleagues (6) demonstrated that the degree of inflammation was dependent upon the number of bacteria in sputum. These pivotal studies with larger numbers of samples show that increased airway inflammation is associated with isolation of bacteria from sputum in COPD. These observations form the basis of ongoing work to elucidate the role of bacteria more precisely in the course and pathogenesis of COPD.

TIMOTHY F. MURPHY

SANJAY SETHI

University at Buffalo, SUNY and VA Western New York Healthcare System
Buffalo, New York

SUSAN L. HILL

ROBERT A. STOCKLEY

Queen Elizabeth Hospital
Birmingham, United Kingdom

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From the Authors:

We appreciate the comments of Dr. Murphy and his colleagues and we would like to reply to the important issues that they mention in their letter. Our study (1) included a thorough microbiologic assessment (including quantitative bacterial cultures from induced sputum and PCR assays for respiratory viruses) of each patient with COPD at three time points: (*1*) at baseline when they were well, (*2*) during the time of an actual COPD exacerbation, and (*3*) one month post-exacerbation. Of the fourteen patients who experienced an exacerbation, a potentially pathogenic bacteria was cultured from the induced sputum sampled at the time of exacerbation from only one of the patients. Cultures from the other 13 patients exhibited only *Neisseria* species, non-pneumococcal alpha-hemolytic *streptopcoccus*, or *Diptheroids* at the time of exacerbation. These bacteria are normal respiratory tract flora and are not respiratory pathogens, therefore they were not judged to be responsible for exacerbation in these patients.

Our study was able to demonstrate that sputum markers of granulocytic inflammation increased, relative to the stable state, in those patients in whom no acute bacterial or viral infection could be demonstrated. However, as Dr. Murphy correctly points out, the number of patients in our study in whom infection was definitively established was small. Therefore we were careful not to make any conclusion about the magnitude of change seen in inflammatory markers in infected patients. We simply concluded that patients with clinical exacerbations of COPD, in whom airway infection cannot be demonstrated, appear to have significantly increased sputum levels of granulocytic inflammatory markers relative to their stable state.

A recently published study by Sethi and colleagues (2) does suggest that COPD exacerbations in which *H. influenzae* or *M. catarrhalis* is cultured from sputum are characterized by higher sputum levels of TNF-α and neutrophil elastase than COPD exacerbations in which these bacteria are not cultured. This study did not compare sputum markers within individual patients at times of clinical stability relative to times of exacerbation. Therefore the Sethi study presents complementary data that do not conflict with the results of our study. We agree with Dr. Murphy's comments that further studies, using longitudinal assessment of patients, at times of clinical stability and at times of exacerbation, are necessary to elucidate the role of bacteria more precisely in the pathogenesis of COPD exacerbation.

SHAWN D. AARON

JONATHAN B. ANGEL

ROBERT E. DALES

The Ottawa Hospital
Ottawa, Ontario, Canada

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THE SCIENCE OF DESIGNING ETHICAL CPAP TRIALS

To the Editor:

In their editorial, Karlawish and Pack (1) raised important and difficult issues. We agree that the problems are real but believe their analysis is one-sided, excessively favoring sham CPAP as the placebo of choice. We have been wrestling with these issues for many years and indeed published in this area (2) well before Wright and colleagues (3).

We do not believe there is a perfect placebo for CPAP since a perfect placebo must be absolutely indistinguishable to the patient. However, because offering treatment to patients with the obstructive sleep apnea/hypopnea syndrome (OSAHS) produces such a large placebo effect—which is seen equally with placebo tablets (4) or sham CPAP (5), both lowering Epworth Sleepiness Score by 2 and significantly improving quality of life—it is vital that carefully controlled trials are carried out and that patients believe they may be receiving active treatment. Indeed, it is uncontrolled trials that are arguably the least ethical since patients are inconvenienced to produce no interpretable results.

We have adopted the placebo tablet approach, whereas Jenkinson and colleagues (5) used "sham CPAP," which was specifically designed to be in-

effective. One could argue that both research groups set out to specifically deceive the treatment population, as we both knew that our "placebo" was ineffective but could not tell the patients this. In this regard, there is no difference between the deception with placebo tablets or sham CPAP. We have been very careful not to mislead patients at any point and have had the full support of our Ethical Advisory Committee. After our two most recent studies (6, 7), we have written to all the patients to inform them that a placebo was used as suggested (1) and none have expressed concern.

Some of the reasons we originally adopted an oral placebo no longer pertain. Specifically, there was an early report that sub-therapeutic CPAP could worsen hypoxemia (8), which has now proven to be unfounded. We thus believe that there is a role for sham CPAP but are concerned that this approach, like the use of placebo tablets, has limitations. Placebos should have no effect on the variable under study, whereas sleeping with an ineffective CPAP machine attached to your face is likely, particularly in mild patients, to perturb sleep and could alter daytime function, artificially impairing the comparators for active treatment below baseline values, thus biasing in favor of active treatment. Our oral placebo will have no effect on the variables under study. The nocturnal discomfort of the mask system presumably explains why Jenkinson and colleagues (5) had lower CPAP use ($p = 0.035$) in their sham CPAP group than in the active CPAP group. This decreased use occurred despite these patients having very severe OSAHS with a median of thirty 4% desaturations/hr in comparison to a median of seven 4% desaturations/hr in our recent study that stimulated the Editorial (6), and four 4% desaturations/hr our mild patients (9). We are concerned that less severe patients might show even lower use of sham CPAP compared to active CPAP, indicating that this would not be a true placebo. We designed our original studies to try to determine the threshold of severity above which patients with OSAHS benefit from therapy, and to achieve this it is the study of mild patients that is most important. This was one of the reasons why we chose an oral placebo and remain concerned that sham CPAP might not be ideal in less severe patients. As a side issue, the editorial is surprising in its statement that "data are not as convincing for mild disease" in view of the three controlled trials showing benefit (4, 9, 10), two of which were published in this journal (4, 10).

The ethical issues are difficult and there is no perfect placebo to a CPAP machine; but the important scientific message is that whatever control system is used, all studies show clear benefits in favor of CPAP therapy for symptoms, quality of life, mood, objective sleepiness, driving simulator performance, cognitive function, and nocturnal sleep (2, 4, 5, 7, 9–13). It is important that skeptics do not lose this message behind a smokescreen of ethical difficulties and dilemmas.

Neil J. Douglas
Heather M. Engleman
Jacqueline F. Faccenda
Nigel McArdle
The University of Edinburgh
Scotland, United Kingdom

1. Karlawish JH, Pack AI. Addressing the ethical problems of randomized and placebo-controlled trials of CPAP. *Am J Respir Crit Care Med* 2001;163:809–810.
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From the Authors:

In response to our editorial (1) about the design of a CPAP clinical trial by Faccenda and colleagues (2), Douglas and colleagues suggest that a discussion of the ethics of sham controls in CPAP research obscures the message that all studies show clear benefits in favor of CPAP therapy for a variety of clinical endpoints. To the contrary, we believe that this discussion illuminates important issues.

A major issue is what control should we test CPAP against: a placebo pill or sham CPAP? Douglas and colleagues claim a placebo pill is best because it has "no effect on the variable under study." But what are we really trying to measure when we use a control? The absolute effect of treatment is equal to the effect of active agent minus the effect of control. Arguably, a sham CPAP informs us of the true absolute effect of treatment because both active and control groups experience the same discomforts of the mask and its gadgetry. Clearly, however, data are needed. We repeat our editorial's conclusion (1): the study that needs to be done is a comparison of CPAP, sham CPAP, sham placebo pills, and other viable "controls." Even more useful would be to randomize subjects to true versus false disclosure that they are receiving active CPAP. Of course, after these studies, the investigators should debrief subjects individually about the design and its results.

A second major issue is whether the data for efficacy of treatment of mild to moderate sleep apnea are less well-established than for severe apnea. A recent Pro-Con Editorial in the *American Journal of Respiratory and Critical Care Medicine* discussed this (3, 4). Dr. Douglas and colleagues cite studies that raise an important question: what is the desired outcome of CPAP therapy? Their own studies (5, 6) show significant improvement using a crossover design in self-reported sleepiness, a depression score, some aspects of quality of life, but no difference in objectively measured sleepiness. It is unlike the results of sham CPAP-controlled trials in patients with more severe disease where improvements in subjective sleepiness concur with improvements in objective sleepiness (3, 4).

These results raise an important ethical and scientific question: what defines benefit of CPAP when one finds improvements in only subjective but not objective assessment of sleepiness?

Jason H. T. Karlawish
Allan I. Pack
University of Pennsylvania
Philadelphia, Pennsylvania

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